VOLUME 50 NUMBER 4

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OF

DERMATOLOGY AND SYPHILOLOGY

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8. Fungous infections of the non-hairy skin	____	____
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- Primary Syphilis
- Miscellaneous
- Primary and Secondary Syphilis—Mixed
- Secondary Syphilis
- Tertiary Syphilis
- Lymphogranuloma—Granuloma Inguinale
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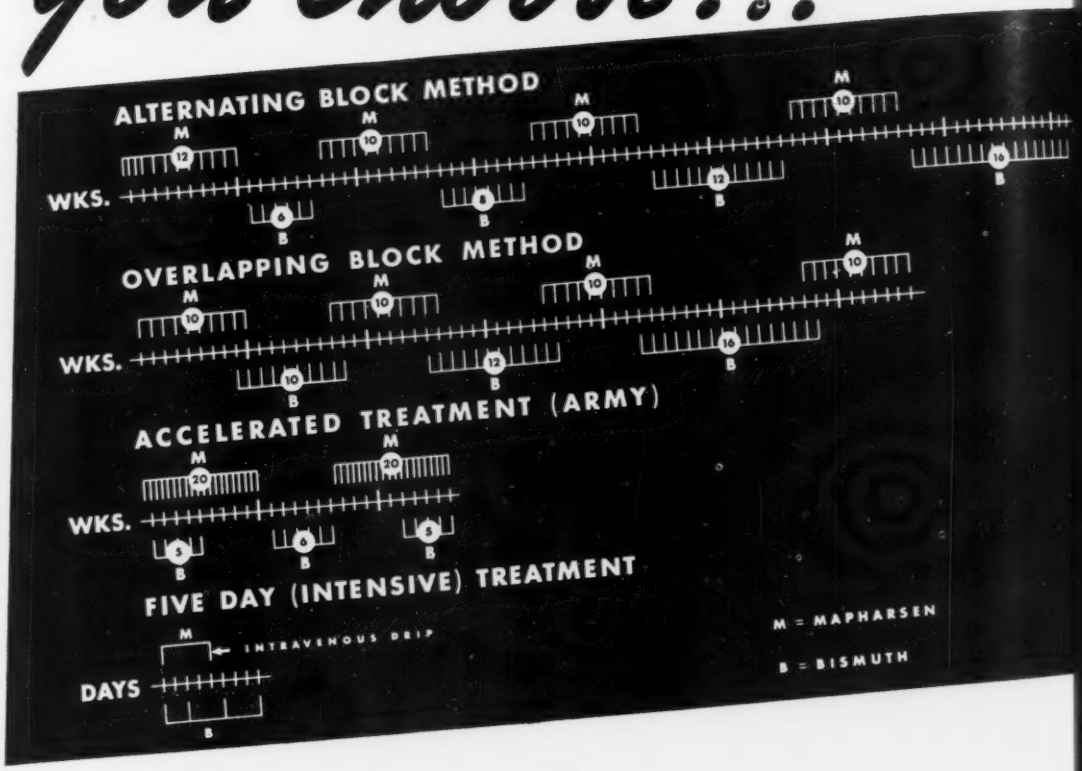

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- Cheilitis glandularis
- Chromidrosis
- Clavus
- Condylomata acuminata
- Cornu
- Dermatitis exfoliativa
- Dermatitis herpetiformis
- Dermatitis (infectious eczematoid)
- Dermatitis papillaris capillitii
- Dermatitis seborrhoeica
- Dermatitis venenata
- Dermatophytosis
- Dermatophytide
- Eczema
- Epithelioma (basal cell)
- Epithelioma (prickle-cell)
- Epithelioma (multiple benign)
- Erysipelas
- Erythema induratum
- Favus (of the scalp)
- Folliculitis decalvans
- Furunculosis
- Granuloma fungoides
- Granuloma pyogenicum
- Granulosis rubra nasi
- Hodgkin's disease
- Hydrocystoma
- Hyperidrosis
- Hyperkeratosis of palms
- Hypertrichosis
- Impetigo
- Intertrigo
- Keloid
- Keratosis (arsenical)
- Keratosis follicularis
- Keratosis seborrheica
- Keratosis senilis
- Kraurosis vulvae
- Lepra nodosa
- Leukemia cutis
- Leukoplakia
- Lichen chronicus (Vidal)
- Lichen nitidus
- Lichen planus
- Lichen scrofulosorum
- Lichenification
- Lupus erythematosus
- Lupus miliaris disseminatus
- Lupus vulgaris
- Lymphadenitis cutis
- Lymphangioma circumscriptum
- Lymphangitis (chronic or recurr streptococcic)
- Molluscum contagiosum
- Mycosis fungioides
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- Nervux pilosus
- Onychomycosis
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- Paronychia
- Pernio
- Pityriasis rosea
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- Pityriasis rosea
- Pompholyx
- Prurigo
- Pruritus
- Psoriasis
- Rhinophyma
- Rhinoscleroma
- Rosacea
- Sarcoid
- Sarcoma (general types)
- Sarcoma (giant cell)
- Sarcoma (Kaposi)
- Scrofuloderma
- Sebaceous cyst
- Sporotrichosis
- Sycosis (lupoid)
- Sycosis vulgaris
- Synovial lesions of the skin
- Syringoma
- Tinea barbae
- Tinea capitis
- Trichophytosis profunda
- Tuberculide (various types)
- Tuberculosis orificialis
- Tuberculosis verrucosa cutis
- Verruca plantaris
- Verruca vulgaris
- Xeroderma pigmentosum (keratosi and epithelioma)

*From "Diseases of the Skin"—Dr. Geo. C. Andrews. "X-Ray and Radium in the Treatment of Diseases of the Skin"—Dr. Geo. M. Mackee.

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BRANCHES IN PRINCIPAL CITIES OF U. S. A. AND CANADA

Archives of Dermatology and Syphilology

VOLUME 50 OCTOBER 1944 NUMBER 4

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CUTANEOUS LEISHMANIASIS (ORIENTAL SORE)

II. INCUBATION PERIOD

D. A. BERBERIAN, M.D.

BEIRUT, LEBANON

The incubation period of oriental sore is estimated in days, weeks, months or years. In the majority of instances this period seems to be from two to seven months. Manson-Bahr [1] (1942) stated that sometimes it may be brief, a few days or weeks; this seems to be established by the appearance of the sore within a short time of a subject's arrival in an endemic district or after inoculation. He also stated that it may be as long as fifteen months.

Marzinowsky [2] (1909) was the first to inoculate himself, and a sore developed seventy days after inoculation. Wenyon [3] (1912) inoculated himself with oriental sore in Aleppo, and six and a half months later a papule appeared at the site of the inoculation, whereas Patton [4] (1912) acquired a sore sixteen days after inoculation. Keelan [5] (1913) reported a case in which the sore made its first appearance a year after the patient had left the endemic area. Napier and Halder [6] (1936) reported a case in which the incubation period appeared to be three and a half years.

Lawrow and Duboskoj [7] (1937) reported on eighty-seven inoculations with infectious material obtained from sores containing large numbers of leishmanias. These inoculations were made during 1932-1933, and within a four year period of observation 85 "takes" (97.7 per cent) were recorded, with the following incubation periods:

Incubation Period	Number of Persons	Percentage
3-4 weeks	33	39
5-8 weeks	29	34
3-4 months	16	19
5 months	5	6
10-11 months	2	2

Lawrow and Duboskoj [7] (1937) also reported on two hundred and twenty-six inoculations with suspensions of living Leishmania tropica. The suspensions were prepared by washing with isotonic solution of sodium chloride six to twenty-three day old first to eleventh generation cultures. These experiments were carried out between December 1933 and April 1935 and resulted in 164 "takes" (73 per cent), with the following incubation periods:

Incubation Period	Number of Persons	Percentage
2-3 months	41	25
4-6 months	84	51
7-9 months	30	18
10-12 months	9	6

In 1939 I [8] reported on forty-four inoculations with suspensions of four to fifty day old first to fourth generation living cultures of L. tropica; in this series the incubation period varied from two weeks to six months, and 35 "takes" resulted. Senekji and Beattie [9] (1941) reported on

From the Department of Parasitology, the American University of Beirut.

The first paper in this series (I. Time Required for Development of Immunity After Vaccination) was published in the June 1944 issue of the ARCHIVES (page 833). The third and fourth papers appear in this issue (pages 233 and 234).

1. Manson-Bahr, P. H.: Manson's Tropical Diseases, ed. 11, London, Cassell & Co., Ltd., 1942, p. 200.

2. Marzinowsky, E. J.: Cultures de Leishmania tropica (s. Ovoplasma orientale, s. Helcosoma tropicum) parasite du bouton d'orient, Bull. Soc. path. exot. **2**:591, 1909.

3. Wenyon, C. M.: Some Remarks on the Successful Inoculation of Leishmania Tropica to Man, J. London School Trop. Med. **1**:224, 1912.

4. Patton, W. S.: Preliminary Report on an Investigation into the Aetiology of Oriental Sore in Cambay, Calcutta, India, 1912; cited by Wenyon, C. M.: Protozoology, London, Baillière, Tindall & Cox, 1926, p. 431.

5. Keelan, R. S.: A Case of Bagdad Sores, Showing an Apparently Long Incubation Period, Indian M. Gaz. **48**:146, 1913.

6. Napier, L. E., and Halder, K. C.: The Incubation Period of Oriental Sore, Indian M. Gaz. **71**:723 (Dec.) 1936.

7. Lawrow, A. P., and Duboskoj, P. A.: Ueber Schutzimpfungen gegen Hautleishmaniose, Arch. f. Schiffs- u. Tropen-Hyg. **41**:374, April, 1937.

8. Berberian, D. A.: Vaccination and Immunity Against Oriental Sore, Tr. Roy. Soc. Trop. Med. & Hyg. **33**:87 (June) 1939.

9. Senekji, H. A., and Beattie, C. P.: Artificial Infection and Immunization of Man with Cultures of Leishmania Tropica, Tr. Roy. Soc. Trop. Med. & Hyg. **34**:415 (May) 1941.

200 positive "takes" in a series of inoculations in which 0.15 cc. doses of suspensions of live organisms were used containing 3,000,000 leptomonads per dose. In their series the incubation period varied from two to eight weeks. Katzenellenbogen [10] (1942) inoculated 167 persons. Of this number 82 were inoculated with leishmanias from the spleens of Syrian hamsters infected with L. tropica and 85 with leptomonads from cultures. Of these, 152 subjects were followed for a period of six to ten months, and in 135 of them (90 per cent) a sore appeared at the site of the inoculation after an incubation period which varied from less than a fortnight to more than two months.

Since April 1937 I have frequently used suspensions of living leishmanias from cultures as vaccine to induce artificial immunity against oriental sore. I have also provided suspensions for vaccination to a number of physicians practicing in Aleppo and Bagdad. To date no untoward results have been reported from these vaccinations. Herewith I wish to report on 3 inoculations with exceptionally long incubation periods.

EXPERIMENTAL STUDIES

EXPERIMENT V-74.—On Nov. 29, 1938, 0.2 cc. of a suspension of living leishmanias in isotonic solution of sodium chloride, representing the entire growth of a twenty-nine day old first subculture from a twenty day old primary culture on an N. N. N. slope, was injected intracutaneously into the left thigh 15 cm. above the kneecap. This volume contained approximately 50,000 leptomonads.

On June 28, 1940, eighteen months after the inoculation, the subject noticed a tiny papule at the site of the injection.

On Nov. 20, 1940, the sore was about 14 mm. in diameter. Leishmanias were demonstrated in the smears from the sore.

On March 25, 1941, the sore was 16 mm. in diameter. It was ulcerated and was beginning to regress.

On July 15, 1941, nine hundred and fifty-six days after the inoculation and three hundred and eighty-three days after the appearance of the sore, it had healed and had left a pigmented scar at its site.

EXPERIMENT V-M.J.—On May 10, 1940, a suspension of leishmanias in isotonic solution of sodium chloride was prepared from twenty day old primary cultures grown on slopes of a modified N. N. N. medium. This suspension contained approximately 3,000,000 leptomonads per cubic centimeter. After sterility checks for aerobic and anaerobic bacteria were made, the suspension was sealed in ampules in 0.5 cc. volumes, and the ampules were kept in a carton box on the laboratory shelf at room temperature.

On May 27, 1940, seventeen days after the preparation of the suspension, an ampule was agitated and opened. A loopful of the preparation was examined under the microscope, and occasional motile leptomonads could still be seen in it. Two-tenths cubic centimeter of this suspension was injected intracutaneously into the left thigh of the volunteer 15 cm. above the kneecap. Between May 10 and 27, 1940, the minimum temperature recorded was 15.8 C. and the maximum 38.5 C.

On Nov. 30, 1942, nine hundred and seventeen days or approximately thirty months, after the inoculation the volunteer noticed a tiny papule at the site of the injection.

On June 5, 1943, the papule was about 8 mm. in diameter. Leishmanias were demonstrated in the smears from the sore.

On Dec. 10, 1943, after a brief period of ulceration the sore had healed spontaneously.

EXPERIMENT V-71.—On Nov. 26, 1938, 0.1 cc. of a suspension of living leishmanias, representing one-fourth the growth of a twenty-six day old first subculture from a nineteen day old primary culture on an N. N. N. slope, was injected intracutaneously into the left thigh 15 cm. above the kneecap. This volume contained approximately 50,000 leptomonads.

On June 20, 1943, four years and seven months after the inoculation, the volunteer noticed a small papule on his left thigh which he could not explain. The papule gradually began to grow and become prominent. On Oct. 30, 1943 he remembered having had an inoculation at that place and came to show the lesion to me. At this time the sore was a papule about 8 mm. in diameter. Leishmanias were abundant in the smears from the sore, and the culture was positive for them. At the time of writing the sore is still not ulcerated. It is about 10 mm. in diameter.

COMMENT

In a previous communication [8] I stated that the incubation period of artificially induced sores seems to be dependent on the quantity of inoculum, the depth of inoculation and the individual variability in the degree of susceptibility. My experience since that publication fully confirms this statement. Immunity against induced oriental sore is slow to develop and is not complete until the healing of the sore. Once immunity is fully established, it is relatively permanent. If the artificially induced or naturally acquired sores are treated in the primary stage or are removed by surgical means, no immunity will result and reinfection is possible. The possibility of encountering oriental sores after exceptionally long incubation periods should be kept in mind, especially among troops returning home after a sojourn in regions where oriental sore is endemic.

SUMMARY

In 3 cases artificially induced oriental sores appeared after exceptionally long incubation periods, eighteen, thirty and fifty-six months respectively.

Dr. E. W. Dennis, chairman of the department of parasitology and bacteriology gave valuable advice and read the manuscript.

10. Katzenellenbogen, I.: Vaccination Against Jericho Boil, Ann. Trop. Med. **36**:28 (June) 1942.

CUTANEOUS LEISHMANIASIS (ORIENTAL SORE)

III. PERIOD OF INFECTIVITY OF SALINE SUSPENSIONS OF LEISHMANIA TROPICA CULTURES KEPT AT ROOM TEMPERATURE

D. A. BERBERIAN, M.D.

BEIRUT, LEBANON

It has been shown by Lawrow and Dubowskoj (1937),[1] by Berberian (1939),[2] by Senekji and Beattie (1941) [3] and by Katzenellenbogen (1942) [4] that it is possible to produce oriental sore on any part of the body by injecting a suspension of living culture of Leishmania tropica into the skin. It has also been shown that a naturally acquired or an artificially induced sore will on healing produce sufficient immunity to protect the individual against reinfection. This procedure, however, will necessitate the maintenance of fresh cultures of L. tropica by physicians who may wish to use it as vaccine. As it is difficult to maintain cultures of L. tropica for physicians practicing in outlying districts where oriental sore is endemic or hyperendemic, it becomes necessary to prepare suspensions of live L. tropica in a central laboratory and issue it to those at outlying points. It is important, therefore, to know accurately the duration of infectivity of suspensions of living cultures of L. tropica in isotonic solution of sodium chloride to enable one to give a correct date of validity for the preparations that are sent out.

EXPERIMENTAL STUDIES

Suspensions in isotonic solution of sodium chloride of living L. tropica organisms from seventeen day old fourth generation cultures grown on a modified N.N.N. medium were prepared. The suspensions contained approximately 3,350,000 leptomonads per cubic centimeter. After sterility checks for aerobic and anaerobic bacteria were made, the suspensions were sealed in ampules in amounts of 0.5 cc., and the ampules were kept in a carton box on the laboratory shelf, by preference at room temperature rather than in the refrigerator because of the fact that in many areas in which oriental sore is endemic refrigerators are either nonexistent or exceedingly rare.

Eleven volunteers were used in this experiment. Just before use, an ampule was opened and a loopful of the culture suspension was examined under a cover slide for the presence of motile leptomonad forms. The inoculations were made intracutaneously in 0.1 and 0.2 cc. quantities, unexposed parts of the body being utilized for the site of inoculation. The anterior aspect of the thigh and the lateral aspect of the hip were the sites used. This experiment was carried out between May 10 and Aug. 13, 1940. During this time the room temperature fluctuated between 15.8 and 33.5 C. except on May 19, on which day there was an exceptional heat wave and the temperature rose to 38.5 C. The results of this experiment are given in the accompanying table.

Results

Volunteer	Age of Culture Suspension, Days	Motile Leptomonads Present or Absent	Temperature Range Between Preparation and Use, C.	Mean Temperature, C.	Results
1	2	P	15.8 - 25.1	20.4	+
2	3	P	15.8 - 33.5	20.6	+
3	7	P	15.8 - 33.5	21.8	+
4	10	P	20.8 - 31.6	22.8	+
5	10	P	20.8 - 31.6	22.8	+
6	10	P	20.8 - 31.6	22.8	+
7	10	P	20.8 - 31.6	22.8	+
8	14	P	20.8 - 33.5	22.5	+
9	17	P	15.8 - 38.5	22.4	+
10	20	A	20.8 - 32.7	22.4	—
11	42	A	15.8 - 38.5	23.3	—

CONCLUSIONS

When a suspension of living culture of L. tropica in isotonic solution of sodium chloride was kept at room temperature varying between 15.8 and 38.5 C., with no special precautions other than avoidance of direct exposure to sunlight, the vaccine was found to be infective for seventeen days from the date of its preparation and to be not infective after twenty days.

A test for the motility of the leptomonads of L. tropica in the suspension will give adequate information about the viability of the organisms.

Dr. E. W. Dennis, chairman of the department of parasitology and bacteriology, gave valuable advice and read the manuscript.

From the Department of Parasitology, The American University of Beirut.

1. Lawrow, A. P., and Dubowskoj, P. A.: Ueber Schutzimpfungen gegen Hautleishmaniose, Arch. f. Schiffs- u. Tropen-Hyg. **41**:374-379 (April) 1937.

2. Berberian, D. A.: Vaccination and Immunity Against Oriental Sore, Tr. Roy. Soc. Trop. Med. & Hyg. **33**:87-94 (June) 1939.

3. Senekji, H. A., and Beattie, C. P.: Artificial Infection and Immunization of Man with Cultures of Leishmania Tropica, Tr. Roy. Soc. Trop. Med. & Hyg. **34**:415-419 (May) 1941.

4. Katzenellenbogen, I.: Vaccination Against Jericho Boil, Ann. Trop. Med. **36**:28-32 (June) 1942.

CUTANEOUS LEISHMANIASIS (ORIENTAL SORE)

IV. VACCINATION AGAINST ORIENTAL SORE WITH SUSPENSIONS OF KILLED LEISHMANIA TROPICA

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BEIRUT, LEBANON

It has been shown by Lawrow and Dubowskoj [1] (1937), by Berberian [2] (1939), by Senekji and Beattie [3] (1941) and by Katzenellenbogen [4] (1942) that lasting immunity against oriental sore can be induced artificially by inoculating susceptible human beings intracutaneously with suspensions of living cultures of Leishmania tropica in isotonic solution of sodium chloride as well as with infective material obtained from early sores on patients. The present paper discusses attempts to induce immunity by the use of a killed vaccine.

During 1938 and 1939 I used as vaccine a phenolized suspension of leishmanias. Freshly isolated local strains of tropica grown on a modified N. N. N. medium were used. The cultures varied from six to eight day old primary cultures to fifty day old fourth generation subcultures. The leishmanias were suspended in 0.5 per cent phenolized saline solution. This concentration of phenol killed the organisms in about seventy-two hours. I injected the vaccine into a group of 32 susceptible volunteers and later tested their immunity by infecting them with suspensions of living leishmanias. It was found that this vaccine did not prevent the development of sores. My results are in agreement with those of Malamos [5] (1937), who failed to immunize hamsters agains Leishmania donovani by inoculating them with suspensions of living avirulent cultures, and with those of Parrot [6] (1929), who failed to immunize Macacus inus monkeys against oriental sore by the use of suspensions of killed as well as living but avirulent cultures of L. tropica. Recently Pessôa [7] (1941) and Pessôa and Pestana [8] (1941) published their results on the successful vaccination against American mucocutaneous leishmaniasis with the use of a killed vaccine. Their vaccine consisted of a suspension of 11 strains of Leishmania braziliensis grown on N. N. N. medium. As the vaccine used by them was comparable to that which I used in my series of experiments, I find it significant to publish my negative results.

In my former paper on "Vaccination and Immunity Against Oriental Sore" [2] (Berberian, 1937), I reported 80 per cent successful "takes" in 44 inoculations. Since then, using the same method, I have made 220 more inoculations, with 92 per cent successful "takes," and have prepared and provided several hundred doses of vaccine to practitioners in different parts of Syria, Lebanon and Iraq. I began preventive vaccination against oriental sore in 1937. Since then none of the inoculated persons now living in hyperendemic areas of oriental sore have reported any sores by natural infection, which confirms my contention that artifically induced or naturally acquired oriental sores confer a lasting immunity to inoculation with infective leishmanias and presumably to infection by natural routes.

EXPERIMENTAL STUDIES

Altogether, 40 volunteers were used in these experiments. Thirty-two volunteers were divided into three

From the Department of Bacteriology and Parasitology, The American University of Beirut.

1. Lawrow, A. P., and Dubowskoj, P. A.: Ueber Schutzimpfungen gegen Hautleitsmaniose, Arch. f. Schiffs- u. Tropen-Hyg. **41**:374-379 (April) 1937.

2. Berberian, D. A.: Vaccination and Immunity Against Oriental Sore, Tr. Roy. Soc. Trop. Med. & Hyg. **33**:87-94 (June) 1939.

3. Senekji, H. A., and Beattie, C. P.: Artificial Infection and Immunization of Man with Cultures of Leishmania Tropica, Tr. Roy. Soc. Trop. Med. & Hyg. **34**:415-419 (May) 1941.

4. Katzenellenbogen, I.: Vaccination Against Jericho Boil, Ann. Trop. Med. **36**:28-32 (June) 1942.

5. Malamos, B.: Versuche mit Leishmanien: Immunisierungsversuche von Hamstern mit Kulturen und Immunseren; Der Einfluss von Kaninechenimmunserum auf das Wachstum verschiedener Kulturen, Arch. f. Schiffs- u. Tropen-Hyg. **41**:416-422 (May) 1937.

6. Parrot, L.: Sur la vaccination contre le bouton d'orient, Compt. rend. Soc. de biol. **100**:411-412, 1929.

7. Pessôa, S. B.: Profilaxia da leishmaniose tegumentar no estado de São Paulo, Folha med. **22**:157-161 (July 25) 1941.

8. Pessôa, S. B., and Pestana, B. R.: Ensaio sobre a vaccinação preventiva na leishmaniose tegumentar americana, com germes mortos, Arq. de hig. e saude púb., São Paulo **6**:139-147 (Jan.) 1941; abstracted, Trop. Dis. Bull. **39**:674 (Oct.) 1942; A intradermoreação de Montenegro nas companhas sanitárias contra a leishmaniose, Arq. de hig. e saude púb., São Paulo **6**:125-137 (Jan.) 1941; abstracted, Trop. Dis. Bull. **39**:673-674 (Oct.) 1942.

roups, each group receiving one, two and three doses f the killed vaccine respectively. The remaining 8 olunteers were used as controls. The injections were ade intracutaneously in 0.2 cc. quantities and were iven at intervals of four to six weeks. This quantity ntained approximately the whole growth of a single ube of N. N. N. culture giving an abundant growth, nd it contained approximately 5,000,000 leptomonads. The site of the injections was the anterior or lateral spect of the thighs about 12 to 15 cm. above the knee-ap. At intervals of thirty-one to three hundred and ixty-seven days after the first dose of the killed accine, the volunteers were inoculated with 0.2 cc. of uspension of living leishmanias containing approxi-nately 2,000,000 leptomonads. Of the 8 volunteers in he control group, 4 are recorded as "susceptible" con-rols, meaning that they have had neither natural nor rtificial immunity. They served as controls to deter-ine the infectivity of the suspension of living culture sed to test the immunity of the subjects vaccinated ith the killed vaccine. The remaining 4, recorded as immune" controls, were persons who have had oriental ore either by natural infection or by artificial immuni-ation. They served as controls to compare their mmunity with that of the subjects vaccinated with the illed vaccine.

Of the 32 volunteers used in the experiment proper, received a single injection of the killed vaccine. At ntervals varying from thirty-one to three hundred and ixty-seven days after the vaccination, they were inocu-ated with 0.2 cc. of suspension of living leishmanias. In these 9 volunteers, as well as in the "susceptible" ontrols injected with the same lot of viable culture uspension, typical oriental sores developed. Eight of he volunteers received two doses of the killed vaccine four to six weeks apart. At intervals varying from ixty-nine to one hundred and thirty-seven days after he injection of the first dose of the killed vaccine, they were each given 0.2 cc. of suspension of living leish-manias. These 8 volunteers and the "susceptible" con-rols all acquired typical oriental sores. Each of the remaining 15 volunteers received three doses of the killed vaccine at intervals of four to six weeks. Later, at intervals varying from one hundred and six to one hundred and fifty-two days from the date of the first dose of vaccine, they were each given a single dose of 0.2 cc. of suspension of living leishmanias. These per-sons and the "susceptible" controls also acquired oriental sores. None of the 4 volunteers registered as "immune" controls had a sore within the observation period of five years.

COMMENT

These experiments clearly showed that the killed vaccine that I used did not produce enough immunity to protect the "susceptible" volunteers against artificial inoculation, whereas natural infection or artificially induced sore produced a definite and solid immunity which protected the "immune" volunteers against the inoculation of large doses of living L. tropica.

In view of my negative results with killed L. tropica vaccine and the recent successful reports of Pessôa[7] (1941) and Pessôa and Pestana[8] (1941) with killed L. braziliensis vaccine, I wish to discuss their results. Unfortunately, it was not possible for me to obtain their original papers. According to the information available in the abstracts given in the *Tropical Diseases Bulletin,* Pessôa, in São Paulo, Brazil, on three occasions at weekly intervals, injected a killed vaccine into 527 persons shown to be nonimmune by the "Montenegro" skin test. Their vaccine consisted of a suspension of cultures from 11 strains of L. braziliensis grown on N. N. N. medium. Of these 527 persons, 17 subsequently acquired cutaneous leishmaniasis, but 5 of them did so in less than a month after vaccination, a period which was in the author's opinion too short for the development of satisfactory immunity. Of 444 vaccinated persons who were followed up in 12, or 2.7 per cent, the disease developed later than one month from the time of vaccination, whereas of 683 unvaccinated nonimmune persons used as controls, 108, or 15.6 per cent, contracted the disease in the same time. Later in one district of Alta Paulista in Brazil Pessôa and Pestana (1941) vaccinated 263 persons subcutaneously and observed 600 persons as controls. During the course of the following four months in 50 of the controls, the disease developed while in only 3 of the vaccinated persons did it do so. Their figures gave an infection rate of 1 per cent for the vaccinated against 8 per cent for the unvaccinated persons.

I am not able to explain their results. I used as vaccine suspensions of L. tropica, and they used suspensions of L. braziliensis. These two species of leishmanias being closely related in their morphology, in their antigenic constitution and in the type of lesions caused by them, it was therefore reasonable to expect an identical or a comparable response to inoculation with either of the organisms. Strikingly Buss[9] (1929) showed that L. tropica gave identical reactions when used as antigen in the "Montenegro" skin test for Brazilian leishmaniasis as antigen prepared from L. braziliensis. This was also confirmed by Pessôa and Pestana (1941).

Senekji and Beattie[8] (1941) have already shown, and my results confirm it,[10] that in naturally acquired as well as artifically induced oriental sores immunity is slow in developing. It begins to appear during the regressive stage of the sore and is not complete until the sore is healed. I am not aware of studies published on the incubation period of American (mucocutaneous) leishmaniasis. In oriental sore the

9. Buss, G.: Untersuchungen mit Leishmania-Vakzine, Arch. f. Schiffs- u. Tropen-Hyg. **33**:65-83 (Feb.) 1929.

10. Berberian, D. A.: Studies on Cutaneous Leishmaniasis (Oriental Sore): I. Time Required for the Development of Immunity After Vaccination, Arch. Dermat. & Syph. **49**:433 (June) 1944.

incubation period is stated to be two to seven months, although exceptionally it may be as short as a few weeks (Manson-Bahr) or as long as fifty-six months.[11] In kala-azar the incubation period has been stated to be usually from six weeks to four months. Here, again, occasionally it may be as short as ten days (Manson) or as long as eighteen months or longer[12] (Napier). American (mucocutaneous) leishmaniasis is quite similar to oriental sore and is indistinguishable from it in cases not associated with nasopharyngeal involvement; it is, therefore, reasonable to infer that its incubation period must also be variable and rather long. An oriental sore begins at first as a pinpoint macule. It grows slowly and becomes a papule. Frequently it is not noticed or is not recognized as such by the person acquiring it until after several months have elapsed. Taking all these points into consideration, I find a period of four months of observation subsequent to three weekly doses of vaccine, as reported by Pessôa and Pestana, too short a period of observation for experiments on leishmania infections, especially so because the value of their vaccine was ascertained entirely by the protection given against natural infection during the period of four months following vaccination and no attempt was made to test the immunity of the vaccinated persons against artificial infection. Their results would have been much more significant if the period of observation could have been extended over a number of years.

In the light of my experiences with preventive vaccination against oriental sore with freshly prepared suspensions of living L. tropica, I wish to report on two recent modifications in my technic.

(*a*) *Site of Inoculation.*—Formerly I used the anterior or lateral aspects of the thighs. I found that the sores in these sites are apt to be large because of strong muscular contractions during walking and exercise. There is also the frequent possibility of bumping the sore and breaking its crust. Therefore I recommend as an alternate area either the loins or the abdomen or the lateral aspect of the os innominatum, where the skin is less likely to be overstretched. At such sites the sores are usually smaller and on healing leave less extensive scars.

(*b*) *Dosage and Volume of Inoculation.*—I have found that 0.05 cc. of suspension containing approximately 50,000 to 100,000 living leishmanias is an ample dose to produce a sore. I have noted that the smaller the dose of leishmanias the longer is the incubation period. The size of the scar produced, however, is mainly dependent on the degree and duration of secondary infection during the ulcerative stage of the sore, and the volume of the inoculum.

CONCLUSION

A L. tropica vaccine was prepared by killing leishmanias from cultures with 0.5 per cent phenol in isotonic solution of sodium chloride. This vaccine when injected intracutaneously in 0.2 cc. amounts in one, two and three doses at monthly intervals did not induce acquired immunity against oriental sore. It was confirmed that the only sure way to acquire a solid immunity against this disease is either by natural infection or by an artifically induced sore. The immunity is complete after the healing of the sore.

Dr. E. W. Dennis, chairman of the department of parasitology and bacteriology, gave valuable advice and read the manuscript.

11. Berberian, D. A.: Studies on Cutaneous Leishmaniasis (Oriental Sore): II. The Incubation Period of Oriental Sore, Arch. Dermat. & Syph., to be published.

12. Napier, L. E., and Halder, K. C.: The Incubation Period of Oriental Sore, Indian M. Gaz. **71**:723-724 (Dec.) 1936.

CUTANEOUS LEISHMANIASIS ON THE ISTHMUS OF PANAMA

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The diagnosis of cutaneous leishmaniasis in 6 patients within one year has been the stimulus for this report. The only articles dealing with cutaneous leishmaniasis on the Isthmus of Panama are 4 case reports, all published over thirty years ago, by Darling,[1] Herrick,[2] Darling and Connor [3] and Bates.[4] Brosius [5] has recorded 2 proved cases from the western part of Panama near Costa Rica. The distribution of cutaneous leishmaniasis in Central and South America has been summarized by Shattuck.[6]

In the forty year period from May 1904 to May 1944 there have been over 500,000 admissions to Gorgas Hospital and over 40,000 surgical specimens have been examined at the Board of Health Laboratory, Ancon, Canal Zone. From these records I have been able to collect 15 cases of proved cutaneous leishmaniasis. The data of these cases are summarized in the table. Only those instances in which the parasites were definitely identified in smears or histologic sections have been included. Several cases in which the appearance of the lesions and the response to specific therapy justified a clinical diagnosis have been omitted. Although most of the patients were not native Panamanians, all had been on the Isthmus over seven months before acquiring the infection, and therefore the cases may be considered autochthonous. Two cases in which the infection probably had been acquired in Colombia were omitted; in 1 of these the nasopharynx was involved. The incubation period has not been recorded in the table because information on this point was so unsatisfactory. In the few instances in which the data seemed reliable the incubation period was in terms of weeks rather than months. Several patients stated that the lesions started as insect bites which enlarged slowly and then ulcerated.

COMMENT

All of the patients were adult males of various races who acquired the disease in the jungle, or "bush," of Panama generally in a manner associated with their occupation. None of the infections were acquired in the sanitated areas of the Canal Zone or in the terminal cities of Panama or Colon. The tendency for cases to occur in groups can be correlated with the degree of "jungle activity" on the Isthmus. Cases 1 to 5 occurred during the construction of the canal, 4 of the patients being employees who worked under "bush" conditions and 1 being a "bush" farmer. The soldiers whose cases are recorded as cases 7 to 9 acquired their infection while on maneuvers, 2 in 1937 and 1 in 1938. The recognition of 6 infections (cases 10 to 15) during the past year is undoubtedly associated with the recent increase in military activities. Seven of the last 9 patients were soldiers.

Most of the lesions were first noticed in the dry season months of January and February. Five patients recalled bites by large flies, mosquitoes and sandflies. The exact distribution of Phlebotomus, considered by many the vector of leishmaniasis, has not been studied locally, but according to Fairchild [7] these small flies are "fairly abundant and widespread in Panama." It is well known that sandflies are more numerous in unsanitated than in sanitated areas.

The infrequency with which these cases occur suggests that there may be an animal reservoir of leishmanias in the jungle. Person to person transmission even with the intervention of an insect vector is unlikely considering the scarcity of cases. Dr. Herbert C. Clark, in monthly visits in the interior, has seen only sporadic cases of leishmaniasis, probably less than 1 a

From the Board of Health Laboratory, Gorgas Hospital, Ancon, Canal Zone.

1. Darling, S. T.: Oriental Sore in Panama, Arch. Int. Med. **7**:581-597 (May) 1911.

2. Herrick, A. B.: An Unusual Type of Oriental Sore, Proc. M. A. Isthmian Canal Zone (pt. 2) **3**:21-25, 1911.

3. Darling, S. T., and Connor, R. C.: A Case of Oriental Sore (Dermal Leishmaniosis) in a Native Colombian, J. A. M. A. **56**:1257-1258 (April 29) 1911.

4. Bates, L. B.: Leishmaniasis (Oriental Sore) of the Nasal Mucosa, Proc. M. A. Isthmian Canal Zone (pt. 2) **5**:83-84, 1913.

5. Brosius, O. T.: Dermal Leishmaniasis—Case Report, in Sixteenth Annual Report of the United Fruit Company Medical Department, 1927, pp. 162-163; Dermal Leishmaniasis, in Nineteenth Annual Report of the United Fruit Company Medical Department, 1930, pp. 107-108.

6. Shattuck, G. C., The Distribution of American Leishmaniasis in Relation to That of Phlebotomus, Am. J. Trop. Med. **16**:187-205 (March) 1936.

7. Fairchild, G. B.: An Annotated List of the Bloodsucking Insects, Ticks and Mites Known from Panama, Am. J. Trop. Med. **23**:569-591 (Nov.) 1943.

year. During a visit to Darien Province, however, in 1930 he saw 3 patients with typical ulcers. Only a few patients with the disease have been treated in the Hospital de Panama or in the Hospital Santo Tomas. To the best of my knowledge, the natives have no special name for the disease, as they do for their more common afflictions.

Nine of the patients had solitary ulcers; 6 had multiple lesions. The mucous membrane of the nasopharynx was involved in 1 patient (case 5[4]). The sites of predilection were the external ear and dorsum of the forearm, wrist and hand. Treatment with antimony and potassium tartrate or fuadin was efficacious. The Wassermann or Kahn tests of the blood elicited negative reactions in 11 patients and a doubtful reaction in 1.

A striking clinical feature of several cases was the presence of a nodular lymphangitis in the areas draining the ulcers similar to that mentioned by Fox.[8] Painful lymphangitis was also noticed, occasionally before the ulcer appeared.

Parenthetically, the difficulties of diagnosis may be mentioned. Diligent, repeated examination of smears and sections taken from the margins of the ulcers, beneath and lateral to the overhanging rim of epithelium, was often necessary before the diagnosis could be established. Diagnosis was not made without the finding of typical parasites with well defined nuclei and the all-important parabasal rods.

TABLE 1.—*Summary Data*

Case No., Year	Sex, Age, Race	Occupation	Place Infected	Month Lesions Noticed	Time Before Diagnosis	Method of Diagnosis	Number, Location and Size of Lesions	Wassermann Reaction	Treatment and Result
1[1] 1910	M, 44, Negro	"Bush" farmer	"Bush" near Empire	May (?)	3 mo.	Smears and sections	1, wrist (2.2 × 1.7 cm.)	Not done	Excision; not stated
2[2] 1910	M, 53, Negro	Surveyor's helper	Bohio ? Gatun ? San Pablo ?	?	2 yr.	Smears and sections	10, ear, chin, forearms, legs, buttock, scrotum, etc. (2 - 5 cm.)	Not done	Excision; recurrences
3[3] 1910	M, 43, Colombian	Surveyor's helper	"Bush" near Frijoles	?	6-8 mo.	Smears	2, left ear (3 cm., 1.5 cm.)	Not done	Not stated
4 1911	M, 27, American	Assistant engineer	Culebra (?)	Feb.	2 mo.	Smears	1, ear	Not done	Excision and cautery; improved
5[4] 1912	M, 35, Panamanian	Farmer	San Carlos ?	?	3 yr.	Smears	9, nasal septum, ears, nose, cheeks, elbows, etc.	Negative	Left before treatment
6 1925	M, 32, American	Storekeeper near "bush"	San Miguel Bog	Dec.	1 mo.	Smears	1, ear (2 cm.)	Negative	Antimony and potassium tartrate; improved
7 1937	M, 41, American	Soldier	Cativa (on maneuvers)	Feb.	3 mo.	Sections	1, forearm (1.5 cm.)	Negative	Excision and antimony and potassium tartrate; cured
8 1937	M, 20, American	Soldier	Cativa ? (on maneuvers)	Feb.	5 mo.	Smears and sections	1, dorsum of hand (2 cm.)	Negative	Excision and antimony and potassium tartrate; cured
9 1938	M, 19, American	Soldier	Cativa (on maneuvers)	March	2 mo.	Sections	3, dorsum of wrist and hand (1.5 - 3 cm.)	Negative	Antimony and potassium tartrate; cured
10 1943	M, 28, American	Soldier	Chorrera (on maneuvers)	Oct.	2 mo.	Sections	1, dorsum of wrist (2.5 cm.)	Negative	Fuadin; cured
11 1943	M, 25, American	Soldier	La Joya (on maneuvers)	March	2 mo.	Sections	1, upper eyelid (1 cm.)	Negative	Fuadin; cured
12 1944	M, 18, Puerto Rican	Soldier	Jungle near Madden Dam	Jan.	2 mo.	Sections	2, forearm (2 - 3 cm.)	Negative	Antimony and potassium tartrate; cured
13 1944	M, 22, American	Soldier	Traveled widely in Panama	Feb.	1 mo.	Sections	1, leg, lower third (3 × 2.5 cm.)	Negative	Antimony and potassium tartrate; cured
14 1944	M, 52, Panamanian	Laborer	Arraijan ? (after creosote burn of nose)	Feb.	6 wk.	Sections	1, over bridge of nose and cheeks (10 cm.)	Doubtful	To be reported later
15 1944	M, 37	Laborer	Camp Caleta, near Ft. Randoph	Jan.	3 mo.	Sections	4, arm, forearm, shoulder, leg (2 - 4 cm.)	Negative	Antimony and potassium tartrate; cured

SUMMARY

Records of 15 cases of cutaneous leishmaniasis acquired on the Isthmus of Panama between 1910 and 1944 were collected and summarized. In 1 instance the mucous membrane of the nose was involved. All of the patients were adult males who became infected in the jungle, or "bush." Treatment with antimony and potassium tartrate or fuadin was efficacious.

NOTE.—Since this paper was submitted for publication an endemic focus of leishmaniasis has been found in Arraijan, Panama. A report will be published in the *American Journal of Tropical Medicine* by Dr. Carl M. Johnson.

8. Fox, H.: American (Mucocutaneous) Leishmaniasis, in Bercovitz, Z. T.: Clinical Tropical Medicine, New York, Paul B. Hoeber, Inc., 1944, p. 240.

VACCINATION AGAINST ORIENTAL SORE

REPORT OF RESULTS OF FIVE HUNDRED AND FIFTY-FIVE INOCULATIONS

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In 1942 I reported the results of a systematic attempt to inoculate the inhabitants of a hyperendemic area against oriental sore.[1] The region comprised the settlements at the northern end of the Dead Sea, and most of the subjects were workers at the Palestine Potash Plant, situated in this area. The problem of oriental sore arose when some hundreds of workers and their families came to settle here, and since then the incidence of sores has steadily increased, so that now the region can be properly called hyperendemic. This sudden increase in morbidity in endemic districts is known; Hovnanian, of Aleppo, (1937) [2] and Shah, of Delhi, (1941) [3] have reported similar incidents.

In the first 167 cases results were encouraging.

It was my belief that it should be possible to sanitate an area by immunizing its inhabitants against the sore. The following factors were considered:

1. All settlers who had never been naturally infected with leishmanias and all newcomers remaining at the Dead Sea during the sandfly season were to be vaccinated. In this way as many persons as possible would have sores at the same time and thus acquire immunity.

2. A single sore would develop instead of the dozens of naturally occurring ones.

3. The vaccination sore would be on a spot usually unexposed (10 cm. above the knee).

The last two factors are of importance, since the possibility that sandflies would become infected from human lesions is thereby considerably reduced. Gerbils and marmots, which, according to Russian authors (Pavlovsky [4] and Latyshev and Kriukova [5]), are "the main source of human infection under desert conditions," are unknown at the Dead Sea. Neither are dogs of any importance as a source of infection. It may be assumed with certainty that in this region it is human beings with oriental sores who are the main source of infection.

There follows a report of results obtained in attempts to vaccinate 556 persons against leishmaniasis.

MATERIAL USED FOR INOCULATIONS

During the first year I used suspensions of cultures on Locke serum agar of Leishmania tropica isolated from local patients and of leishmania bodies of the same strain from the spleens of infected Syrian hamsters. The use of the latter was undertaken for experimental purposes,[1] but, although it proved successful, it was later discontinued.

METHOD

Inoculations were made on the anterior surface of the thigh about 10 cm. above the knee. One-tenth cubic centimeter (containing approximately 1,500,000 active flagellates) of a culture suspension was injected intradermally.

SUBJECTS

In addition to the 167 subjects reported on in the previous paper, 389 persons were inoculated. From Jan. 14 to April 6, 1941, 182 persons were inoculated; between Nov. 12, 1941 and March 31, 1942, inoculations were given to 218, and between Dec. 16, 1942 and April 9, 1943, 156 persons were vaccinated—a total of 556.

From the Dermatologic Department, Bicur Holim Hospital, and the Workers' Sick Fund Outpatient Department.

1. Katzenellenbogen, I.: Vaccination Against Jericho Boil, Ann. Trop. Med. **36**:28-31 (June) 1942; abstracted, Harefuah **22**:136-137 (May) 1942.

2. Hovnanian, P.; Jebejian, R., and Yenikomshian, H. A.: Dermal Leishmaniasis in Newly Inhabited Section of Aleppo, Tr. Roy. Soc. Trop. Med. & Hyg. **31**:191-198 (July) 1937.

3. Shah, M. H.: Report on Epidemic of Oriental Sore in Delhi, Indian M. Gaz. **76**:449-457 (Aug.) 1941.

4. Reservoir Hosts of Cutaneous Leishmaniasis, Report of the Scientific Research Work of All-Union Institute of Experimental Medicine for 1938-1939, Moscow, 1940, pp. 108-109; abstracted, Trop. Dis. Bull. **39**: 538 (Aug.) 1942.

5. Latyshev, N. I., and Kriukova, A. P.: On the Epidemiology of the Cutaneous Leishmaniasis: The Cutaneous Leishmania as a Zoonotic Disease of Wild Rodents in Turkmenia, Trav. Acad. mil. méd. armée Rouge U. S. S. R. **25**:229-241, 1941; English summary, pp. 241-242.

Included among the subjects were 11 children and 1 pregnant woman. The subjects ranged in age from 3 months to 74 years.

Four hundred and sixteen of the patients were followed up; 82 are still under observation. In 237 persons an oriental sore was produced.

Since a number of my subjects were workers who left their employment during the period, the percentage of patients followed up is smaller than that of other authors who have reported results of vaccinations (Lawrow and Dubowskoj [6] and Senekji and Beattie [7]). On the other hand, I have been able to follow the greater number of my subjects during a period of three years, and I have therefore been able to check the results of my vaccinations.

INCUBATION PERIOD

The period of incubation varied from less than a fortnight to eighteen months. While for the majority of subjects the period was from four to six weeks, for 2 it was five months; for 2, six months; for 1, eight months; for 1, ten months; for 1, fourteen months, and for 1, eighteen months. In some patients for whom results were previously reported as negative the characteristic sore developed on the site of the previous inoculation.

That the incubation period for the same person may vary is shown by the following case:

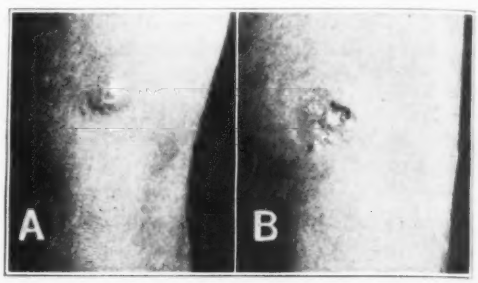
CASE 1.—The first inoculation was made on Jan. 2, 1942, and there was no sign of inflammation or sore until March 2, 1943. On March 3, one day after the appearance of the sore, a second inoculation was made. On March 24, that is, after an incubation period of three weeks, a typical nodule containing numerous parasites appeared on the site of the second inoculation. From this it appears that whereas the first sore required an incubation period of fourteen months the second needed one of only three weeks.

SPECIFIC LESIONS

At the end of the incubation period a bluish red papule appears, varying in size from that of a lentil to that of a pea (fig. *A*). There is often light scaling at the tip. Pain is usually absent. The papule persists for three to six months and then heals, leaving behind a small scar. Sometimes, however, pea-sized infiltrates are formed which have a purulent depression in the center resembling a small ulcer (fig. *B*). The papules are sensitive to injury and can often be converted into ulcers by slight trauma or by scratching; for that reason I have ceased to divide these artificial sores for statistical purposes into nodules and ulcers.

In 3 cases there were formed around the main sore small shallow ulcers which were assumed to be due to traumatic secondary infection and which, unlike the main lesion, cleared when a dressing of ordinary solution of boric acid was applied.

In only 1 case was a leishmania nodule formed directly on the site of the healing vaccination sore.



Experimental oriental sore produced by intracutaneous injection of cultures of living L. tropica. *A*, dry lesion; *B*, moist lesion.

CASE 2.—The patient was inoculated on March 11, 1943, and on May 5 a sore the size of a pea appeared. It opened and closed several times, finally healing in October 1943, when there appeared around the edge of the site of the previous lesion four new papules the size of lentils. In one of these papules leishmanias were easily found. All of the papules cleared fourteen days later, leaving shallow scars. It must be assumed that scratching of the vaccinated area carried some of the material into the adjacent area, giving rise to the papules, or that the inoculated material entered the lymphatics, causing so-called metastases around the sore. A natural infection around the artificial sore had also to be considered; but this hypothesis was discarded in view of the rapid healing of the papule and the fact that it appeared after the vaccination sore healed.

It is true that new papules may occasionally develop in the old scars or at the margin of an oriental sore in a patient with so-called relapsing leishmaniasis; but these lesions are characterized by chronicity, and, besides, they contain few or no parasites. Neither was true in this case.

In rare cases the artificial sore differs from the usual form described.

CASE 3.—A 2 year old girl was vaccinated with leishmania bodies on Nov. 14, 1941. A nodule appeared after six weeks. As a result of trauma there appeared six weeks later a slow-healing flat ulceration of the size of a child's palm, clinically resembling scrofuloderma. It cleared three months later, leaving a thin scar.

6. Lawrow, A. P., and Dubowskoj, P. A.: Ueber Schutzimpfungen gegen Hautleishmaniose, Arch. f. Schiffs- u. Tropen-Hyg. **41**:374-379 (April) 1937.

7. Senekji, H. A., and Beattie, C. P.: Artificial Infection and Immunization of Men with Cultures of Leishmania Tropica, Tr. Roy. Soc. Trop. Med. & Hyg. **34**:415-419 (May) 1941.

VACCINATION OF CHILDREN

Eleven children were vaccinated, the youngest being 3 months old. Except in the case reported in the previous paragraph, the course was the same as in adults. Special precautions were taken with children, especially with infants, to cover the sore and thus protect it from scratching or other trauma.

Five infants were vaccinated at the Kwuzath Halugim settlement, none of whom became infected, whereas 6 infants born during the sand-fly season and therefore not vaccinated acquired numerous sores on the body, face and hairy scalp.

REACTION FOLLOWING INOCULATION

Altogether 45 persons showed a reaction after vaccination. Twelve to twenty-four hours after vaccination there was swelling at the site of injection, and sometimes there was infiltration of an area the size of a palm. The temperature rose to 103 F. There was moderate pain at the site of injection, with occasionally tenderness of the inguinal lymph nodes. The condition did not last more than one to three days and never ended in abscess formation.

Of the 45 persons inoculated only 4 acquired vaccination sores. In the remaining 41 the infiltrate disappeared within ten to fourteen days without leaving a scar.

ANALYSIS OF CASES

Of the 45 subjects 26 had been at the Dead Sea for several years. They could give no definite information about previous leishmania sores. Most showed scars on the arms or legs. Sores are of frequent occurrence at the Dead Sea, but it is impossible to establish their causation with certainty from scars.

The fever and swelling indicate an allergic reaction to a further introduction of parasites. Such reactions following vaccination in persons previously infected with leishmanias have been described by other authors as well as by me.

NATURAL IMMUNITY

In 27 persons who had been living several years at the Dead Sea and who showed no obvious signs of healed sores, vaccination did not produce a "take," and the patients had no reaction either on the day following inoculation or later. Seven of these were inoculated on two subsequent occasions, with the same negative result. In these persons the possibility of natural immunity to leishmanias must be considered.

REINFECTION

On various occasions I was told by patients at the Dead Sea that they had twice had oriental sore, the second often occurring after an interval of seven years. I know of only 1 certain case, and this I reported on in an earlier publication. In other cases observed by me there was no positive microscopic evidence for either the first or the second sore.

ARTIFICIAL REINFECTION

I succeeded in obtaining artificial reinfection in 2 patients vaccinated immediately after the appearance of the first sore. Unlike Senekji and Beattie,[7] I have not been able to obtain a successful vaccination with the ordinary volume of material in patients with naturally acquired leishmaniasis of more than four months' duration. Infiltrates the size of a cherry appeared without fever or pain, disappearing in a few days or weeks.

I think that in certain cases in which a second infection with oriental sore was said to have occurred the papules were but the expression of a late reaction of the skin to a new introduction of parasites by bites of infected sand-flies or by vaccination. The same negative results were obtained in cases of so-called leishmaniasis recidiva for which "disturbance of immunity and lack of resistance" have been held responsible (Dostrowsky [8]).

In spite of their lack of immunity, I was unable to reinfect such patients, as may be seen from the following cases.

CASE 4.—A. M., a boy aged 13, from Ramallah (16 kilometers north of Jerusalem), had an eruption which had started three years previously with small papules at first slowly healing at the center and forming new sores at the periphery. When I first saw him he had a lesion the size of a child's palm on the left cheek below the lower eyelid, having a scar at the center and small bluish red papules, some covered with adherent scales, at the margin. Parasites were not found on microscopic examination, but organisms were obtained on culture. On March 25, 1943 he was vaccinated with 0.1 cc. of a culture of leishmanias. Twenty-five hours later there was reddening and swelling (6 by 4 cm.) at the site of inoculation. The swelling increased in the following two days. On March 28 the swelling was the size of a hand and was painful. On March 29 signs began to abate. On April 2 there was infiltration over an area the size of a walnut at the site of injection, with a small hemorrhagic vesicle at the top. In the course of the next seven days this disappeared, leaving a small scar.

In this patient relapsing leishmaniasis therefore followed the same course of reaction to

8. Dostrowsky, A.: Relapses in Cutaneous Leishmaniasis, in Deliberationes Congressus Dermatologorum Internationalis, Budapest, 1936, vol. 2, pp. 610-617; Ann. Trop. Med. **30**:267-274 (Oct.) 1936.

vaccination as in persons who had been previously infected and were immune.

In the second case the course was different, resembling that of a reinfection.

CASE 5.—D. M., a 26 year old woman from Afghanistan, soon after her arrival in Palestine, eight years ago, acquired an ulcerous leishmania sore on the right cheek and near it sores healing at the center and spreading at the margin. Other parts of the cheek became affected during the following eight years. Microscopic examination did not reveal L. tropica, but cultures became positive after three weeks (instead of the usual six or seven days). On Jan. 13, 1943 the patient was vaccinated with 0.1 cc. of a culture of leishmania organisms. Twenty hours later there was a pinkish raised area at the site but no pain. On the next day there was slight tenderness at the site of inoculation and the infiltration had increased somewhat. All signs disappeared within the next two days leaving only slight tenderness on pressure at the site. On Feb. 7 (four weeks after the inoculation) there was a bluish red, painless, noninflammatory nodule as large as a bean at the site of inoculation. Parasites were not found on microscopic examination or by culture. The nodule was removed and examined histologically.

The histologic examination revealed a focus of fibrous tissue with vascular dilatation and small areas of chronic perivascular inflammation. There were large inflammatory areas at the periphery. Elastic fibers were completely missing in the connective tissue, and there was hypertrophy of the epidermis without extension into the papillae. Smears of the section did not show leishmanias. The cutaneous changes therefore were not those of leishmania, and this nodule was the product of a leishmania reaction.

The only remarkable feature about this case is the late appearance of the reaction (four weeks instead of the usual two or three days).

In 3 other cases of oriental sore in which vaccination was performed six to eight months after the appearance of the natural boil a similar late reaction has occurred. These nodules are characteristized by absence of parasites in the smears and cultures and, further, by quick disappearance (few days or a week).

NATURAL INFECTION IN SPITE OF INOCULATION

Nineteen cases of natural infection in spite of inoculation were observed. In 9 cases inoculation was made during the incubation period of the vaccination. In 7 cases previous inoculation had not produced a "take." Natural infection appeared during the following sandfly season (April to November). In 3 cases natural infection appeared during the existence of the inoculation sore.

From the point of view of success of inoculation, the last observation is the most important. Were the liability to natural infection before inoculation and during the existence of the sore equal, it would be out of the question to expect any practical success for an inoculation campaign; for one has to wait more than a year for immunity to be established, during which time natural infection would almost certainly occur in this hyperendemic area in spite of vaccination. The success of my inoculations proves these apprehensions groundless.

The number of patients from the potash plant with oriental sore was reduced to an insignificant figure in 1943.

The most reliable figures are those from the settlement of Kwuzath Hahugim, situated north of the potash plant. Here the settlers are permanent. The follow-up is thus easier and more accurate. In the last two years 95 new settlers have been added to the settlement. Only 25 of these were vaccinated, and not 1 of them became infected. Of the 70 remaining, 65 became infected.

Twenty persons vaccinated unsuccessfully in 1941 did not acquire a natural infection in the next two years. In 5 persons in whom the first vaccination did not produce a take a vaccination sore developed after the second inoculation.

THERAPY

Leishmaniasis induced by vaccination requires no special treatment. I found covering the sore or painting it with brilliant green (tetraethyldiaminotriphenylmethane silver) enough. The sore lasts from two months to a year.

CONCLUSIONS

Five hundred and fifty-six persons were vaccinated against oriental sore, and 416 persons were followed up. In 237 of them a vaccination sore developed after an incubation period varying from less than a fortnight to eighteen months.

This vaccination has considerably reduced the incidence in a hyperendemic region.

Vaccination should be carried out four to five months before the sandfly season begins.

As expected, there were cases of natural infection during the incubation period of a natural infection or natural infection during the incubation period of an artificial leishmania infection.

Vaccination was found harmless, even for infants, and practically painless. It gave the persons vaccinated a good chance of prophylaxis against numerous sores in exposed areas.

Reactions after vaccination were due to a previous infection with L. tropica.

Artificial reinfection was successful in 2 persons vaccinated immediately after the appearance of the first sore.

I could not obtain a real vaccination sore in cases of relapsing leishmaniasis.

TREATMENT OF TRICHOPHYTOSIS WITH ETHYL CHLORIDE

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Our interest in the treatment of trichophytosis of the feet, hands and groins with ethyl chloride was revived by a recent article in the ARCHIVES OF DERMATOLOGY AND SYPHILOGY.[1] Ethyl chloride was extolled as a simple, effective and safe remedy for all varieties of dermatomycosis without the necessity of considering severity, degree of inflammation or complication by secondary bacterial infection. One of us had occasionally used ethyl chloride, with indifferent results. It was found to be useful as an adjunct to apparently more reliable methods of treatment, particularly as a modality for promoting dryness of the skin, but in no instance by itself did it produce clinical eradication. Perhaps it had not been given a sufficient clinical trial. It occurred to us that we might be, therefore, disregarding a valuable therapeutic procedure.

As there were at Bushnell General Hospital numerous patients with dermatomycosis suitable for the evaluation of ethyl chloride spray as a therapeutic procedure, a more extensive trial with this agent was considered worth while. The purpose of this paper is to summarize our experience from its exclusive use for 40 unselected consecutive ambulatory and bed patients. A large majority of these patients were observed in the outpatient department. Only 6 had infections of sufficient severity to require hospitalization. The management of all groups was identical.

All of the patients had trichophytosis of the interdigital spaces, soles, palms or crural regions, usually involving the toes and soles but occasionally also the hands and groins. The lesions were clinically characteristic, and their objective appearances were considered diagnostic even when not substantiated by laboratory studies. In 1 case the disease was clinically and culturally moniliasis. Since there is an active antifungus program in force at Bushnell General Hospital, resulting in a remarkably low percentage of infections, all of the patients reported on had received previous treatment. This may explain the low incidence of positive cultures and the occasional complete absence of laboratory confirmation.

The procedures adopted for this investigation consisted of examination of scales prepared in 20 per cent solution of potassium hydroxide, implantation of scales on Sabouraud's medium and administration of intradermal trichophytin sensitivity tests before treatments were commenced. The technic of applying ethyl chloride as described in the previously mentioned article [1] was followed as closely as possible. This consisted of spraying all lesions and approximately 1 cm. of surrounding clinically normal skin until a distinct frosting was effected which required approximately one minute to melt. The degree of frosting varied with the type of skin treated and the relative inflammation of the lesions. Treatments were originally planned for ten consecutive days because it was stated that the most severe infection usually responded within ten days. However, in order to evaluate this method of treatment, when complete subsidence was not produced by ten applications the treatments were extended to an average of fourteen days and in some instances as long as twenty-six days. All patients were inspected ten days after the last treatment, and examinations of potassium hydroxide–treated scales were repeated at this time.

Ethyl chloride produces immediate burning and stinging, particularly as the area defrosts. There was no case, however, in which treatment was discontinued because of this discomfort. The usual inflammatory reaction was increased for the first two to three days. Reassurance that the treatments were not making the eruption worse was necessary in many cases. Increased experience showed that proper technic of application is important. If liquid ethyl chloride, which unavoidably collects on the skin when the spray is too heavy and evaporation is not sufficiently rapid, runs onto the normal skin, particularly on the dorsa of the feet at the base of the toes, there results a dermatitis congelationis. The lesions produced vary from simple erythema to vesicles and bullae. They were uncomfortable but healed uneventfully within three or four days. This complication from treatment is prevented by having the patient hold paper towels on the

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1. Bograd, N.: Treatment of Tinea with Ethyl Chloride, Arch. Dermat. & Syph. **48**:511 (Nov.) 1943.

normal skin around the infected areas when the ethyl chloride is applied.

All varieties of lesions were treated, from superficial dry scales to extensive vesicular, pustular and denuded areas showing secondary bacterial lymphangitis. Ethyl chloride may be sprayed on these raw areas without ill effects or undue discomfort, and it produces surprisingly quick healing. No attempts were made at epithelial débridement. In all except a few instances, the patients reported improvement within a few days. This was particularly noted as a subsidence of pruritus. The superficial vesicles, secondary pustules and denuded areas regressed usually after the sixth to the eighth application. Two patients with extremely chronic infections, showing deep-seated plantar vesicles, experienced continued activity with the formation of vesicles while under treatment, notwithstanding heavy applications of ethyl chloride, insuring complete freezing of the epidermis. Several persons exhibiting clinical trichophytids of the palms experienced rapid relief from the pruritus and a remission of the lesions as both the primary infections on the feet and the palmar lesions were treated with ethyl chloride. In the 1 case of moniliasis no response to ethyl chloride therapy was shown. Excessive dryness was produced, followed by increased scaling and peeling, apparently a result of the inflammatory reaction caused by the ethyl chloride. As with all medications directed toward fungous infections, the acute, vesicular lesions seemed to respond more dramatically than the chronic, dry types. A number of patients presented varying degrees of hyperhidrosis. This always regressed while being treated with the ethyl chloride.

When the active treatments were completed, definite improvement was observed in practically all cases, and the patients were enthusiastic about the procedure. We shared their enthusiasm, and had we written this paper at this stage of our study our conclusions would have confirmed those previously reported. But when the patients returned for follow-up examinations ten to fifteen days after their treatments had been discontinued and during which time they had received no antifungus medication, practically all showed continuous active infections. The majority showed improvement, but in many the infection had returned to the vesicular stage, and 1 or 2 required hospitalization when seen at their follow-up examination.

CONCLUSIONS

Ethyl chloride spray, producing distinct frosting of the skin, may be used without harmful effects in the treatment of trichophytosis. It may be applied to all varieties of lesions, including those showing secondary bacterial involvement.

Immediate clinical improvement, with subsidence of vesicles and pustules, healing of denuded areas, increased dryness of the skin and regression of hyperhidrosis, follows the applications of ethyl chloride.

Ethyl chloride does not produce a cure or eradication of trichophytosis. Recurrences are experienced in practically all instances within ten days.

Ethyl chloride may be used with advantage as an adjunct to the customary management of trichophytosis, particularly in the vesicular stage. It apparently promotes dryness of the skin, producing an antagonistic environment for the fungi.

Colonel James S. Sweeney, Medical Corps, Chief of Medical Service, made valuable suggestions in this work.

DERMATITIS FROM TYROGLYPHIDAE IN HANDLERS OF STRAW

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Although infestation with mites of the family Tyroglyphidae has long been recognized as a hazard in certain occupations (handling of cheese, copra, sugar, dried fruits and grains), it either occurs infrequently or is perhaps not diagnosed as such. Feeling that the latter view is the correct one and that the disease warrants fuller recognition, I wish to present my experiences with 2 cases encountered recently.

Tyroglyphidae is a family of the order Acarina, as is also Sarcoptidae. However, unlike Acarus scabiei, members of the family do not burrow into the skin. Their natural habitat is the substances mentioned. On man they cause an eruption, usually limited to the exposed surfaces, which cannot be distinguished morphologically from contact dermatitis of other causation. The history of contact with cheese, copra or one of the other substances mentioned and the demonstration of the parasite on the skin or in the suspected material establish the proper diagnosis.

REPORT OF CASES

CASE 1.—H. M., a man aged 52, had been employed as a shipping and receiving clerk in a hotel and restaurant supply house for thirteen years. One of his chief duties was to remove chinaware from its straw-packed containers. In the summer of 1943 he had an eruption on the face and forearms. Suspecting the straw as the source of his trouble, he quit work for two weeks and the eruption cleared. However, it recurred shortly after he returned to work. He consulted me on Nov. 3, 1943 because of the intense itching, worse at night, on the neck and forearms. Examination showed greatly excoriated urticarial papules at these sites. Grain itch, caused by Pediculoides ventricosus, was suspected although the lesions lacked any characteristic central vesication. Applications of a sulfur preparation were prescribed but the itching became more intense; so its use was discontinued, and soothing applications were substituted. Nevertheless, he became highly nervous from the itching and insomnia and had to be hospitalized. Since the eruption then cleared promptly, his clothing was regarded as the probable source of reinfestation. When told that the straw was probably responsible for his dermatosis, he quit his job and obtained a different one.

At about this time, the Division of Industrial Hygiene of the United States Public Health Service was called in by the employer to investigate the straw. The inspectors reported discovering mites in the siftings of the straw. These mites were later identified as a species of Tyroglyphidae by an entomologist from the United States Department of Agriculture, Washington, D. C.

CASE 2.—W. K. W., aged 67, a fellow employee of H. M. (case 1), had been employed in the same shipping department for three years. He handled the straw packing material only occasionally. His symptoms developed at about the same time as those of H. M. The eruption was comparatively mild, and he found that avoidance of the straw prevented most of the trouble. However, in February 1944 the eruption became so troublesome that he consulted me for relief. Examination (February 22) showed a splotchy erythema of the middle of the face and lichenified erythematous excoriated papules on the volar surfaces of the wrists. The diagnosis of mite dermatitis was confirmed when he told me that the straw which he handled was of the same batch in which the inspectors had found parasites. Soothing preparations were prescribed, and he made a satisfactory recovery. According to his statements, attempts were being made to rid the premises of all the infested straw.

COMMENT

In 2 cases of dermatitis from infestation with grain mites the history of contact with straw suggested a parasitic factor, later identified as tyroglyphid mites by entomologists of the United States Department of Agriculture. It is felt that such eruptions are more common than is realized, apparently not being recognized as such. The topical use of sulfur may be the cause of a superimposed dermatitis, as the course in case 1 suggests (the clearcut picture of sulfur rash was not present). While avoidance of contact with infested straw is the best means of prevention, the parasites could be killed by exposure to dry heat at 150 F., according to information from the United States Department of Agriculture.

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PENICILLIN IN TREATMENT OF SIMULTANEOUS INFECTIONS OF SYPHILIS AND GONORRHEA

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Penicillin is the first therapeutic agent which has been found to be effective against both syphilis and gonorrhea. The amount of the drug used in treating gonorrhea, however, is usually about 100,000 units, a much smaller amount than that required in the treatment of syphilis, usually over 1,000,000 units. The use of penicillin for patients who have contracted gonorrhea and syphilis simultaneously will undoubtedly lead to unusual changes in the course of the syphilitic infection.

A patient acquiring both diseases simultaneously will probably first present symptoms of gonorrhea, since the period of incubation of this disease is usually shorter than that of syphilis. If such a patient is treated with the amount of penicillin given for gonorrhea, he is also receiving a small amount of antisyphilitic drug during the period of incubation of syphilis. The biologic changes which are likely to occur may be compared to those found in patients receiving a few injections of arsphenamine during the period of incubation of the disease. This procedure, known as "prophylactic treatment," has not been recommended by American authorities, since it may only suppress and not eradicate the infection. According to Moore [1] such a patient may remain free of lesions and the Wassermann reaction remain negative for years and subsequently late lesions involving the nervous system or the cardiovascular apparatus may appear. In the case here reported the patient received 50,000 units of penicillin, not during the incubation period but on the same day that the primary lesion was noted. The patient was then in the seronegative stage. The insufficient amount of treatment received healed the lesion for two weeks, but relapse occurred subsequently.

REPORT OF A CASE

A 22 year old white noncommissioned officer was admitted to the urologic clinic on Dec. 9, 1943 because of a urethral discharge in which gonococci were found. The last sexual contact was on November 30. One course of sulfathiazole was given while the patient was on duty status and another after he was hospitalized. This treatment failed to control the disease, and he was transferred on December 24 to a general hospital. The patient received 50,000 units of penicillin on Jan. 1, 1944, with immediate improvement of the urethral discharge. He stated that on the day of the treatment he noticed a small papular lesion on the glans penis. Results of dark field examinations for Treponema pallidum were negative on January 3, 4 and 5. The lesion had disappeared entirely by January 8. Kahn reactions were negative on Dec. 31, 1943 and Jan. 6, 1944. On January 17 the patient was returned to duty. On January 19 he noted a minute painless ulcer at the identical place that the former lesion had appeared. There was a shotty nontender inguinal adenitis. There were no other manifestations of syphilis. He reported to the hospital on January 24, and a dark field examination of the lesion showed the presence of Treponema pallidum. A Kahn test on the same day elicited a negative reaction. Routine antisyphilitic therapy was started on that day.

SUMMARY AND CONCLUSIONS

A patient received 50,000 units of penicillin for the treatment of gonorrhea on the same day that a primary lesion of syphilis appeared. A recurrence of a syphilitic lesion was noted three weeks later.

As to the effect of the administration of penicillin for the treatment of gonorrhea on simultaneously acquired syphilis, it is likely that a small amount of penicillin given during the period of incubation of syphilis will suppress or modify the early manifestations of the disease but will fail to prevent its progress. This may result in a latent period followed by late lesions. Unless the amount of the drug administered is increased to cope with both diseases in all cases, which at present is impractical, the period of observation for syphilis of patients with gonorrhea treated with penicillin should be extended at least to one year and preferably much longer. This procedure will detect syphilitic infection which may have been temporarily suppressed.

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1. Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., Charles C Thomas, Publisher, 1933, p. 164.

CHOLINOGENIC URTICARIA AND CHOLINOGENIC ITCHING

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Urticaria induced by physical agents is an infrequent phenomenon but one that has been widely studied. Heat, cold, sunshine, trauma and probably other physical agents are capable of producing it. In persons in whom urticaria is produced by heat the attacks can also be precipitated by exercise and emotional stress. In fact, there is an interaction of these three factors which makes difficult the evaluation of any one of them. Of persons in whom attacks are produced by heat, effort and emotion, there are two groups: those who have urticaria and those who have generalized itching without urticarial lesions. The urticarial group has had the most attention; the second has been neglected, though the fundamental mechanism in each is probably similar.

There has been a tendency to try to explain the reaction in persons with all types of physical urticaria on the basis of release of H substance by the causative physical agent, but this has not been substantiated.

The work of Grant, Pearson and Comeau [1] demonstrated that urticaria from heat, emotion and exercise is different from other physical urticarias in that the attacks can be produced at will by the injection of acetylcholine derivatives. The compound which they used was carbachol (Doryl [carbaminoylcholine chloride]), which has the same physiologic action as acetylcholine, which is not stable.

Hopkins, Kesten and Hazel [2] confirmed Grant's results and reported their findings before this association. Hopkins suggested the name "cholinogenic urticaria" for the syndrome. Grant and associates sought to show by experiments on their patients that acetylcholine acts through the parasympathetic nervous system (cholinergic nerves) to release H substance, which produces the urticaria. Both groups showed that the attacks of urticaria could also be induced by pilocarpine, acting on the parasympathetic nerves.

According to Starling's [3] explanation of the humoral theory of nervous transmission, acetylcholine has its peripheral action on the parasympathetic nerves and also on the preganglionic connections of the autonomic system. These nerves are now often called the cholinergic nerves. The peripheral action gives rise to the most important visible signs of parasympathetic action, i. e., salivation, excessive lacrimation, perspiration and flushing of the face. The action is similar to the pharmacologic action of pilocarpine and opposite to that of atropine.

Neither Grant and his colleagues nor Hopkins discussed the second group, who have generalized itching without urticaria produced by heat, exercise and emotion and whose attacks can be reproduced by acetylcholine compounds. The reaction of these would seem to invalidate the theory that H substance is responsible in all cases for itching from heat, exercise and emotion. That theory is, however, still tenable in regard to persons who have urticaria.

REPORT OF CASES

Four patients were studied who had itching produced by exercise, emotional stress and heat. One had urticaria, and the other 3 had generalized itching produced in the same way but without urticaria.

The first patient was a healthy woman, aged 29, who had had urticaria from heat, exercise and emotional stress for nine years. Her condition was almost the same as that of most of the patients of Hopkins, Kesten and Hazel and Grant and associates. Her urticaria had appeared in a mild form at the age of 20, when she was working in a restaurant at a job in a warm environment. She then noted a few hives on her neck and upper part of the chest when she was hot and flushed from her work. For four years she continued to have mild attacks induced by heat, exercise and emotional stress. Then her attacks became generalized and lasted usually for two to six hours but occasionally twenty-four hours. On two occasions she had angioneurotic edema.

Exercise was the most important inciting agent. One dance would cause generalized hives, and housework, especially ironing, would bring on an attack quickly. Excitement alone could produce an attack but needed,

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Read at the Sixty-Fifth Annual Meeting of the American Dermatological Association, Inc., Chicago, June 20, 1944.

1. Grant, R. T.; Pearson, R. S. B., and Comeau, W. J.: Observations on Urticaria Provoked by Emotion, by Exercise and by Warming the Body, Clin. Sc. **2**:253, 1936.

2. Hopkins, J. G.; Kesten, B. M., and Hazel, O. G.: Urticaria Provoked by Heat or by Psychic Stimuli, Arch. Dermat. & Syph. **38**:679 (Nov.) 1938.

3. Starling, E. H.: Principles of Human Physiology, ed. 8, revised by C. L. Evans, Philadelphia, Lea & Febiger, 1941, p. 367.

as a rule, to be combined with mild work. Heat alone rarely caused an eruption of hives if she was at complete rest, but light work in the warm sun rapidly produced a generalized attack. She gradually learned to limit her activities so that she would have one or two mild attacks a week and a severe one possibly once a month. The severe ones always came when she was nervous and upset. She discovered that when an attack was impending it could be greatly alleviated if she immediately lay down to cool off and took a soda bath followed by complete rest. The longest interval between attacks was seldom more than a month. After a severe attack her face would be flushed, her heart would pound and she would have a slight headache. There was no history of atopic disease in her family, and foods or other things did not cause the attacks. The attacks were induced more easily during her two pregnancies and during her menstrual periods.

On her first visit, on a warm spring day, she had generalized hives caused by the heat of the day and the hurry and excitement of the anticipated visit. She had hives all over her body except the palms, soles, face and axillas. They ranged from numerous lesions 1 to 3 cm. in diameter to large palm-sized confluent hives on her trunk. She stated that the eruption was typical of a severe attack that might last twenty-four hours.

On her next visit, a week later, she was careful not to hurry or get excited and she had no hives on arrival. After a period of rest she was given 12 mg. of mecholyl-chloride (acetylbetamethylcholine chloride) intramuscularly, and in five minutes the usual physiologic effects of salivation, perspiration and other signs developed.

At ten minutes she stated that she "itched all over," but hives did not appear until two minutes later. They appeared first around every hair follicle on her body, as a generalized goose flesh. At seventeen minutes, they had enlarged to 5 mm. in diameter, and shortly they became confluent on her trunk. There were no hives on the face, palms, soles and axillas. At the height of the attack the lesions appeared the same as the spontaneous hives she had on her first visit. The eruption reached its peak after about forty minutes, and forty-five minutes later it was going away, leaving a residual erythema. The patient stated that the mecholyl-induced attack was the same as the more severe spontaneous attacks, except that it was speeded up, coming on more explosively and disappearing more quickly.

Because of the severity of the induced attack, the patient was reluctant to have it repeated. She finally consented to an injection of 5 mg. of pilocarpine hydrochloride. The effect was the same as that of mecholyl. The physiologic effects of salivation and sweating came within seven minutes, and generalized hives of the same type came in fifteen minutes. The attack was, if anything, more severe than the one produced by mecholyl.

A general physical examination revealed normal conditions, and there was no indication of any other abnormality. Attempts at treatment were unsuccessful, but by being careful the patient can keep her attacks minimal.

The remaining 3 patients had generalized itching induced by effort, emotion and heat. Their condition differed from that of the first patient and those reported by Hopkins in several ways. The spontaneous attacks came on more quickly, were more acute and passed off more rapidly and were unassociated with hives, presenting only a slight transient erythema of the skin. They were similar in that mecholyl chloride induced attacks identical with the spontaneous ones.

The first patient of this group was a healthy truck driver, aged 24, who had had his disease for more than a year. The attacks of generalized itching were induced mostly by exercise but occasionaly came on when he was sitting quietly. He had attacks almost every day and might have as many as seven mild attacks in one day.

A typical attack would come on as follows: After ten or fifteen minutes of work in an average temperature, the attack would begin by a feeling as of needle pricking over his entire body, including the palms and soles, but worse on the head, back, legs and chest. The itching would become so intense that he could not sit still, and he would scratch and rub himself all over. The attack would last only fifteen minutes if he could cool off by removing his clothes and dousing himself with cold water but would last much longer if he could not cool off. Heat and emotional stress rarely alone produced an attack, but the frequency and severity of the attacks were greater in hot weather and when he was under mental stress.

He stated that he had one attack while he was loading corn into a truck with the temperature —30 F. and he obtained relief only by stripping to the waist. He said, "That farmer must have thought I was crazy because he ran away." His attacks that came without exercise occurred mostly when he was eating in restaurants. Toward the end of the meal of warm food in a warm room he would feel an attack coming on. He would hurriedly pay his bill and run out to the nearest alley to strip to the waist. When driving a truck on a hot day he might have to stop every 25 miles (40 kilometers) because of a mild attack. If he did not stop and cool off, the attacks would be worse. Whenever possible, he liked to douse himself with cold water to shorten the attack.

On his first consultation he was stripped and allowed to rest and minimize the psychic element. He was not told what I expected to do. He was given 1/170 grain (0.38 mg.) of histamine phosphate intramuscularly, but no reaction occurred. About fifteen minutes later he was given 12 mg. of mecholyl chloride. Within less than a minute he stated that an attack was impending, and he was starting to rub and scratch. Within another two minutes he could remain on the examining table no longer and was in a frenzy of rubbing and scratching. A pitcher of ice water was standing on the table and he poured it over his trunk. The attack subsided in about ten minutes. He said that the induced attack was like the more severe of the spontaneous ones.

Because atropine is physiologically antagonistic to acetylcholine, he was given 1/120 grain (0.54 mg.) of atropine sulfate intravenously about two minutes after the mecholyl, but it did not affect the attack. A second attack was produced by mecholyl, and 0.5 Gm. of theophylline ethylenediamine was given shortly after the injection of mecholyl. The attack was less severe.

Several days later an attempt was made to produce an attack by immersing an arm in hot water. A blood pressure cuff was previously placed on the arm at a pressure greater than the systolic. After four and one-half minutes a very mild attack occurred which passed off in two or three minutes. It is probable that the psychic effect of anticipation of the attack was more important than the external heat. To test the psychic element further the patient was given 1 cc. of distilled

ater but he had the impression he was getting mecho-l. A mild attack that passed off quickly resulted fter one minute and forty-five seconds. A short time ter he was given 12.5 mg. of mecholyl chloride in lution but was told that it was distilled water. The tack came on in fifty seconds and sent him into a enzy of rubbing and dousing himself with cold water. During the next week he took 1/100 grain (0.65 mg.) atropine sulfate four times a day, but it did not crease the number of the spontaneous attacks. He id sufficient atropine to make his mouth dry. He was ven 1 cc. of isotonic solution of sodium chloride, inking it was mecholyl, but no attack was produced. Shortly thereafter 8 mg. of mecholyl chloride produced mild attack.

In all the attacks produced by mecholyl, the subjective sensations began in about a minute but the physiologic effects, sweating, etc., appeared only when the attack was at its height. This is in contrast to the first patient with urticaria, in whom the physiologic effects of mecholyl developed several minutes before the urticaria appeared.

The third patient was a naval officer, aged 33, who had generalized itching produced by exercise and emotion, which had been present for three months. He had had the same condition ten years previously. The attacks of generalized itching would occur whenever he exercised with the cadets, when he lectured to the cadets and during the sexual play preceding intercourse with his wife.

The attacks of itching were moderate and lasted ten to fifteen minutes. They were reproduced by mecholyl in a dose of 12 mg. Except that the attacks were much milder, they were the same as those of the previous patient. Desensitization by repeated injection of mecholyl chloride was attempted, and eight attacks were caused in this way. This had no effect on the severity or number of the spontaneous attacks. Histamine (1/176 grain [0.37 mg.]) elicited no reaction.

The last patient was a man who had had generalized itching for five months. His attacks were provoked by excitement, exertion and external heat. He was seen on only one occasion, at which time no reaction was produced by 1/132 grain (0.5 mg.) of histamine phosphate, but an attack of severe degree was produced by 12.5 mg. of mecholyl chloride. The attack came on in less than two minutes and was at its height when the physiologic effect of mecholyl appeared. Atropine, given under the direction of his family physician, was without effect, as was also histaminase.

A letter from his physician three years later stated that the patient still had attacks produced by a small amount of work and in summer had to spend most of his time in a cool basement. He managed to mow his small lawn by working a few minutes at a time in the cool part of the day, but he could not complete the job in one day. He was completely disabled from gainful work.

Control subjects given injections of mecholyl did not react except in the physiologic manner. These consisted of 2 patients with unexplained generalized itching, several with urticaria of various types and 1 with urticaria from cold.

COMMENT

It would be logical to assume that urticaria or itching produced by exercise, emotional stress and heat is produced by an endogenous substance. Study of these patients shows that generalized itching and urticaria induced by these three factors may be caused by an abnormal reaction to an endogenous substance, i. e., acetylcholine.

This work confirms the conclusions of Grant, Pearson and Comeau and Hopkins, Kesten and Hazel that mecholyl will produce attacks of generalized urticaria in persons who have spontaneous urticaria induced by exercise, heat and emotion alone or in combination. The induced urticaria is the same as that in the more severe of the spontaneous attacks. The time required to produce the urticaria is about ten minutes, and it occurs several minutes after the normal physiologic action of mecholyl. The theory of Grant and associates, that mecholyl acts on the parasympathetic (cholinergic) nerves to release H substance and thus produce the urticaria, offers a good explanation, but the basic cause of the mechanism remains to be determined.

Patients who had generalized itching caused by exercise, heat and emotion but no hives were studied by neither Grant and associates nor Hopkins and associates. The syndrome of these patients is similar, but there are great differences, such as shorter, more frequent and more explosive spontaneous attacks. The great difference in the induced attacks was that they came on soon, two minutes or less, after the injection of mecholyl and before a physiologic effect such as sweating. There was little to see on the skin except slight redness and goose flesh at the height of the attack.

The theory that H substance causes the itching in this group is not tenable because hives are not formed and the attacks come so rapidly after the injection. In this group the acetylcholine derivatives must have a more direct action on the cholinergic nerves of the skin and in some unexplained way produce itching. There is at present no logical explanation why some persons react abnormally to a physiologic substance, such as acetylcholine, which is a vital factor in the functions of the autonomic nervous system. All of the patients also reacted in normal fashion with sweating, salivation, etc., to mecholyl.

SUMMARY AND CONCLUSIONS

Four patients, 1 with generalized urticaria and the others with attacks of generalized itching produced spontaneously by exercise, heat and emotional stress, were studied. Mecholyl, an acetylcholine derivative, reproduced the symptoms in all 4. It was therefore assumed that these disorders were "cholinogenic."

In the production of urticaria, mecholyl probably acts through the mediation of H substance, but in producing generalized itching it must have a direct action on the cholinergic nerves of the skin.

LOCAL TREATMENT OF PSORIASIS BY CHOLINE CHLORIDE

REPORT OF TWO CASES

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Feeding of lecithin in the treatment of psoriasis has been favorably described. Results in a recent controlled hospital study [1] by my colleagues and me justified continued study. In place of lecithin supplied orally over a period, the supposed active fraction, choline chloride, was prepared in pure form and directed into the lesions by iontophoresis.

The technical application of the iontophoresis was by procedures in common use, with the positive pole as the active pole and the negative pole as the inactive. Pure choline chloride in powder state was made up to a 1 per cent solution in water, and an asbestos pad 6 by 6 cm. was soaked with the solution at the positive pole. Isotonic solution of sodium chloride was used to moisten the large asbestos negative pole. Areas of equally severe involvement were used, and the upper extremities found entirely suitable in these cases. The maximum tolerated milliamperage was used.

Two cases were studied. In each the disease was of the intractable type.

REPORT OF CASES

CASE 1.—E. R., a spinstress, had the onset of psoriasis seven years previously, at the age of 46. At one stage she had psoriatic erythroderma, said to follow arsenical treatment. Application of mild tars with ultraviolet irradiation were of slight aid. Feeding of soy bean lecithin on a hospital controlled regimen and low fat diet produced transient improvement in the first two weeks, but subsequent return to the original level occurred despite four months' ingestion, one month of which was in the hospital. The general condition was good, and results of all laboratory studies, including tests of hepatic function, were within normal ranges.

The patient was given iontophoresis of 1 per cent choline chloride seventeen times over a period of three weeks, with maximum tolerated milliamperage, which finally reached 30 milliamperes. Thirty minute exposures were given. During the second week of treatment definite improvement was noted in both arms at the sites of the positive and negative poles. Soon, however, it was noted that the site of the active agent was somewhat improved over the control site. Nevertheless both improved, neither side remarkably, but the site of the choline pole slightly more so. Elsewhere there were no changes in the lesions, though the pruritus became worse.

Choline chloride was then incorporated in a water-soluble ointment base in a 10 per cent concentration. Under hospital observation the medication was rubbed into symmetric lesions of the thighs, the active agent into one and the ointment base alone into the other. Both areas definitely improved for three weeks. Five more weeks of similar application did not produce much further improvement. The site of application of the choline ointment showed slightly greater improvement up to the time that all improvement ceased.

CASE 2.—H. M., aged 47, was a nervous woman who had suffered for the past thirty-five years from severe generalized psoriasis, mild hypertrophic arthritis and varicosities with ulcerations of the legs. There were moderate obesity and a history of some suspected episodes of disease of the gallbladder but no demonstrated hepatic disease. The patient often did well with applications of coal tar preparations and ultraviolet irradiation. Massive doses of ascorbic acid were of no aid. Hospitalization with oral administration of soy bean lecithin in large doses was of no value.

She received iontophoresis thirteen times in fourteen days with no change at either the positive, choline chloride-moistened, pole or at the negative pole, wet with saline solution. Elsewhere, however, the eruption, which already was generalized, confluent and infiltrated, became more extensive from new guttate lesions appearing at all previously uninvolved areas. Application of choline ointment over a period of four weeks resulted in no change.

Obviously these cases are not presented to draw conclusions. They are reported as study technics involving an untried medicament, choline chloride. Perhaps it would be better to use this procedure only on persons shown to respond to lecithin by mouth, with the local technics applied to the more severe lesions.

SUMMARY

Choline chloride iontophoresis was tried on 2 patients with chronic psoriasis who had previously shown no response to oral administration of soy bean lecithin. No striking local or general changes were produced beyond transient local changes about both electrodes.

Use of 10 per cent choline chloride ointment was continued locally for both patients without success.

Dr. Leon Goldman gave helpful advice in the development of this study.

From the Department of Dermatology and Syphilology, College of Medicine, University of Cincinnati.

1. Smith, C. C.; Goldman, L., and Fox, H. H.: Lecithin Feeding in the Syndrome of Psoriasis, J. Invest. Dermat. **5**:321 (Dec.) 1942.

TREATMENT OF ECZEMATOUS CONTACT DERMATITIS WITH INTRAVENOUS INJECTIONS OF SODIUM THIOSULFATE

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PHILADELPHIA

Some years ago Ormsby [1] proposed intravenous injection of sodium thiosulfate as a general desensitizing agent against various factors which were capable of causing contact dermatitis. The proposed technic consisted of five injections of an aqueous solution of the drug administered as follows: first injection, 7½ grains (0.485 Gm.); second injection (twenty-four hours thereafter) 15 grains (0.97 Gm.); third, fourth and fifth injections (given at intervals of forty-eight hours), each 15 grains. The Suttons, commenting on this treatment in the tenth edition of their textbook, stated that they regarded it as being without value.

As numerous patients with contact dermatitis visited the clinic at the Skin and Cancer Hospital of Philadelphia, it was decided to give the treatment a trial. Twenty patients were selected for treatment by this method, and many of them were followed after their return to their work so as to be able to ascertain whether any degree of desensitization was achieved. This series consisted of two groups, one of persons whose eruption had existed for less than six months at the time of consultation and the other of persons whose eruption had lasted for more than six months. In the first group there were 11 patients and in the second 9.

Following is a brief statement of the essential dermatologic facts regarding the patients of group 1:

CASE 1.—S. S., a youth aged 18, worked with paints and turpentine. The duration of the eruption was three months. It was limited to the right palm and consisted of a poorly marginated scaly area with vesiculation. The interspaces of the toes were normal. The patient was given solution of sodium thiosulfate intravenously and a bland ointment, and by the fifth injection the skin had become apparently normal. This occurred within twelve days after the first visit. A request for follow-up information was unheeded by the patient.

CASE 2.—R. H., a youth aged 20, worked with hats. The duration of the eruption was two months. The hands and fingers showed poorly defined patches of vesicles on an erythematous background. Treatment consisted of injections of sodium thiosulfate, and the patient was discharged as well after the fifth injection. Follow-up in two months after his return to work showed no recurrence of the eruption.

CASE 3.—J. S., a man aged 37, worked in a dye plant. For the past three months the dorsal aspect of the hands and wrists had been reddened and crusted, with vesicles here and there and with decided itching. Treatment consisted of the usual series of injections of sodium thiosulfate. There was considerable improvement, but the skin was not normal. Follow-up eight months after the last visit showed that the eruption had lost some of its improvement and was spreading slightly, although the patient was able to continue with his former work.

CASE 4.—E. S., a man aged 28, worked as a grinder. The duration of the dermatitis was three months. It was limited to the hands and consisted of a diffuse eruption of fine papules and vesicles. There was slight scaling in the interspaces of the toes, but direct examination of the material did not reveal ringworm fungi. The patient received the routine injections of sodium thiosulfate, and the eruption responded favorably to the treatment. Follow-up three months later showed no return of the eruption, although small areas of dyshidrotic dermatitis had developed in the cubital areas. This patient had not returned to his former work.

CASE 5.—E. S., aged 29, was a housewife. The eruption developed three months after birth of a baby and consisted of patches of vesicular eruption on the left hand. The interspaces of the toes were clear. Decided perspiration was present. The usual sodium thiosulfate treatment was given, and the eruption cleared. Follow-up eight months therafter showed no recurrence.

CASE 6.—H. G., a man aged 25, worked with chemicals on metals. The duration of the eruption was one week. His arms, hands and fingers were covered with a papular eruption. There was decided subjective discomfort. The usual sodium thiosulfate therapy was prescribed, but the result was rather poor and the patient disappeared from observation. There was no follow-up.

CASE 8.—J. J., aged 60, was a housewife. The duration of the eruption was four weeks. Both arms showed poorly defined areas of erythema and scaling with decided itching. The usual intravenous therapy was administered, with a most favorable result. Follow-up a year later disclosed a decided improvement, with but slight itching at night, although the patient continued to do her work.

CASE 9.—J. A., a man 51 years of age, was a glass worker. The duration of the eruption was five weeks. The lesions affected the fingers, especially the lateral

From the Skin Clinic, The Skin and Cancer Hospital.

1. Cited by Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939.

aspects, and the right palm and consisted of a diffuse erythema and fine vesicles. The feet were normal. The usual treatment was given; the result was good. Follow-up data could not be obtained.

CASE 10.—J. S., a man aged 60, was a soda fountain helper. The duration of the dermatosis was five weeks. The eruption consisted of irregular poorly marginated patches of erythema and vesiculation on the dorsal aspect of both hands, with here and there fissuring and crusting. The usual intravenous treatment was given with good results. Follow-up almost a year later showed that the patient had returned to his work, and, while the skin was not completely normal, there was much less annoyance than before treatment was instituted.

CASE 11.—F. C., a man aged 36, worked around machinery at a refining plant and came into contact with mercury. The duration of the eruption was six weeks. The dorsal aspects of the hands showed vesicles and perifollicular pustules. After the usual intravenous therapy the eruption disappeared. There was no reply to the follow-up questionnaire.

Following is a résumé of the cases of the patients in group *2*:

CASE 12.—C. W., a boy aged 15, worked at a soda fountain. The eruption on the hands was of long duration and consisted of poorly defined patches of erythema and scaling. The usual injections of solution of sodium thiosulfate were given, and the eruption cleared. The follow-up questionnaire four months after completion of treatment showed that the eruption had recurred but slightly and that the patient had resumed his former work.

CASE 13.—J. C., a man 40 years of age, a textile worker, had to have his hands constantly soapy while at work. The duration of the eruption was one year. Both hands showed erythema and scaling. The feet were normal. The treatment consisted of intravenous injections of solution of sodium thiosulfate, and the eruption cleared. Follow-up about one year thereafter showed that although the patient was working at his former job there had been no recurrence.

CASE 14.—A. T., a woman aged 31, was a cigar worker. Her hands were more or less constantly in water. The duration of the eruption was six months. It was vesicular and involved the dorsal and palmar surfaces of both hands. The usual intravenous therapy was given, and the eruption cleared. Follow-up almost a year after treatment showed no return of the eruption, although the patient was employed at the same work.

CASE 15.—G. P., a woman aged 20, was an operator in a beauty parlor. The duration of her eruption was one and a half years. On the dorsal aspect of the hands, especially the left, there were large erythematous patches with exudative crusting and vesicle formation. The usual treatment was given, and the eruption cleared. Follow-up four months thereafter disclosed no return of the dermatosis.

CASE 16.—R. R., aged 50, was a housewife. She had had an eruption on the hands intermittently for one year. The dorsal aspects of both hands showed erythema and scaling with decided itching. Scaling of the interspaces of the toes was present, but direct examination did not reveal ringworm fungi. The usual intravenous treatment was prescribed, and the eruption cleared. Follow-up four months after cessation of treatment showed that the skin remained well although the patient continued to perform her housework duties.

CASE 17.—M. S., a man aged 36, was an electrician. The duration of the eruption was six months. It consisted of poorly defined patches of hyperkeratosis, scaling and fissuring on the palmar aspects of both hands. The patient was treated with sodium thiosulfate intravenously, and the eruption cleared, although in this case, in addition, one intensive dose of roentgen rays was necessary. Follow-up after four months disclosed that the eruption had recurred in part when the patient returned to his former job but was not as intense as previously.

CASE 18.—J. P., a man aged 42, was a machinist working with cutting oil. The eruption was of twenty-two months' duration and involved the back of the hands with patches of erythema, vesiculation and scaling. Sodium thiosulfate therapy yielded a good result but follow-up showed that the eruption returned two weeks after the patient resumed his former work.

CASE 19.—J. McE., a man aged 38, worked with blueprints. About a year and a half before he was seen the tips of several fingers broke out with poorly defined areas of erythema, scaling and vesiculation. Solution of sodium thiosulfate was given intravenously, with but little improvement.

CASE 20.—R. Y., a man aged 33, was a cement worker. About fifteen years before he was seen the right hand began breaking out with irregularly shaped and poorly marginated patches of erythema, infiltration, scaling and vesicle formation. Intravenous administration of sodium thiosulfate yielded a good result, with restoration of the skin to normal except for one small area of infiltration which later disappeared. Inspection of the skin one month after the discharge of the patient showed absence of any cutaneous lesions.

COMMENT

Analysis of the cases reported shows the following results. In the group of 11 patients with acute dermatitis the immediate results were good in 9 instances and in 2 no beneficial effect was noted. So far as permanency of improvement was concerned, such favorable outcome was obtained in 6 instances; in 1 there was a relapse, and 5 patients failed to respond to the questionnaire. In the group of persons whose cutaneous eruptions existed for a period longer than six months, the immediate results were as follows: In 7 cases the cutaneous lesions cleared after the sodium thiosulfate therapy, and in 2 instances the remedy failed. Follow-up investigation of the long range effect of the treatment in this group disclosed that in 6 instances the eruption did not return and in 3 instances relapses occurred. It is to be stated that most of these patients received solution of boric acid for local use. This statement was omitted in the body of the paper, as it was felt that such local treatment could not in the space of ten to twelve days cause a disappearance of the eruptive elements, espe-

cially in the more chronic types, and certainly could not effect any degree of desensitization.

In search for a possible explanation of the results obtained through use of sodium thiosulfate in the eczematous contact dermatitis, consideration must first be given to a possible action of the chemical itself. In this connection, the concept that N. P. Anderson [2] recently expressed in his article entitled "Neutralization as a Therapeutic Principle in Contact Dermatitis" is worthy of recapitulation, for he stressed the desirability and plausibility of chemical neutralization of the causative factor. It seems hardly likely that such small amounts of sodium thiosulfate as given in this treatment could possibly accomplish much in this direction.

2. Anderson, N. P.: Neutralization as a Therapeutic Principle in Contact Dermatitis, Arch. Dermat. & Syph. **49**:176 (March) 1944.

SUMMARY

Intravenous injections of aqueous solution of sodium thiosulfate have been employed in treatment of the eczematous contact dermatitis with good immediate results and with some degree of at least partial desensitization, as evidenced by return of some patients to their previous work without suffering a relapse. The way in which this treatment operates is obscure. The suggestion by Anderson that study of the chemical antidotes for the various agents capable of causing a contact dermatitis is both timely and constructive.

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SCLEROPOIKILODERMA WITH CALCINOSIS CUTIS, RAYNAUD-LIKE SYNDROME AND ATROPHODERMA

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The many unusual complications of the following case of generalized scleroderma with acrodermatitis chronica atrophicans are of such rarity that it is deemed worthy of recording. This case further illustrates the many and varying manifestations of scleroderma, a disease the pathogenesis of which is obscure and the prognosis of which internists today regard as serious, especially in the generalized form.

REPORT OF A CASE

History.—Mrs. A. S., a white woman aged 46, was admitted to the New York Post-Graduate Medical School and Hospital on Jan. 5, 1944, complaining of a generalized eruption of three years' duration and pains in the joints of two years' duration.

Present Illness.—About three years ago a pruritic erythematous and edematous eruption developed on the dorsa of the patient's hands. One week later she became aware of a similar eruption involving the vulva and the perineal and perianal areas. She then consulted her family physician and was referred to a dermatologist, who diagnosed the eruption as eczema. Treatment consisted of topical medication and ultraviolet irradiation. While she was under the doctor's care new lesions appeared on the front of the chest, arms and forearms. The patient was given one roentgen ray treatment to the affected areas, and coincident with this and about four weeks after the onset the eruption became generalized by involving the trunk, thighs and upper extremities. She then consulted a general physician, who treated her with a sun lamp, after which there followed an exacerbation of the entire eruption. Subsequently the treatment consisted of vitamins given orally and parenterally. Two years ago the erythema and edema subsided, leaving pigmented scaly lesions. About this time the patient noticed that her hands, fingers and feet would turn white on exposure to cold and that on standing her feet would turn purple. She next experienced pain with resultant limitation of movement of the wrists, fingers and knee joints. Subsequently ulcers developed over metacarpal-phalangeal joints as well as on the knees and malleoli. These ulcers would discharge grumous material and take about a month to heal.

One year ago the patient began to lose weight and has now lost 40 pounds (18.1 Kg.). Her present weight is 86 pounds (39 Kg.). During the past six months there has been generalized weakness and recurring stu ulcers on the legs. She experiences difficulty in openi her mouth, due to pain in the mandibular joints, a difficulty in swallowing.

Six months ago a scaly eruption developed over t occiput, and later ulcers developed which on heali have left bald spots and general loss of hair.

The patient has been ambulatory since the beginni of her illness.

Past Illnesses.—The patient had pyelitis twelve yea ago and an appendectomy and suspension fifteen yea ago.

Marital History.—The husband is alive and well. S has two children, aged 28 and 26, alive and well.

Menstrual History.—The onset of menstruation wa at 13 years of age. Her menopause began two yea ago, and there have been only two periods in the pa two years.

Skin.—Scalp: There is thinning, especially of th temporoparietal areas. On the occiput to the right o the midline there is a large area of alopecia, orang sized, erythematous, crusted and scaly in areas, sug gestive of lupus erythematosus. The rest of the scal shows small patches of erythema and scaling.

Face: The face is emaciated, the nose beaked, an the veins prominent on the forehead; the skin i atrophic. There are two ulcers on each side of th chin, crusted, yellowish and tender to palpation. Th eyelids show telangiectases. There is a fine telangie tatic scattered erythematous eruption on the face.

Trunk: The skin of the neck, chest (including th breasts except for the nipples and areolas), abdomen an back shows a diffuse reticulated pigmentation ass ciated with telangiectasia and superficial atrophy. Ther are large deposits of calcium in the subcutaneous tissu palpable in the regions of the neck, breasts, shoulder axillas and abdomen and over the iliac crest areas a well as in the anterolateral aspect of the thighs.

Upper Extremities: The skin about the extensor sur face of the elbows shows the fine atrophy and cigaret paper wrinkling typical of acrodermatitis chronic atrophicans. Along the ulnar border of the radius i the vicinity of the elbow there is a deposition of calcium The upper extremities, thighs and perineum show picture akin to "x-ray" skin.

There is evident general wasting. On the elbow an knee areas there are large palpable tender deposits o calcium. Large ulcers are present on the inner aspec of the knees. The legs and ankles show numerou small scars from previous ulcers.

On the dorsa of the hands one sees fine atrophic ski with the underlying veins standing out in bold relief The fingers have the appearance of sclerodactylia bu are soft and supple rather than hidebound.

From the Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University.

Fig. 1.—Scleropoikiloderma of the neck, chest, abdomen and arms anteriorly and scleroderma of the face; beaked nose, and telangiectases.

Fig. 2.—Acrodermatitis chronica atrophicans involving the extensor surface of the elbow and deposits of calcium in the "ulnar band."

Fig. 3.—Atrophy, ulceration and calcareous concretion over the fourth metacarpal phalangeal joint of the right hand.

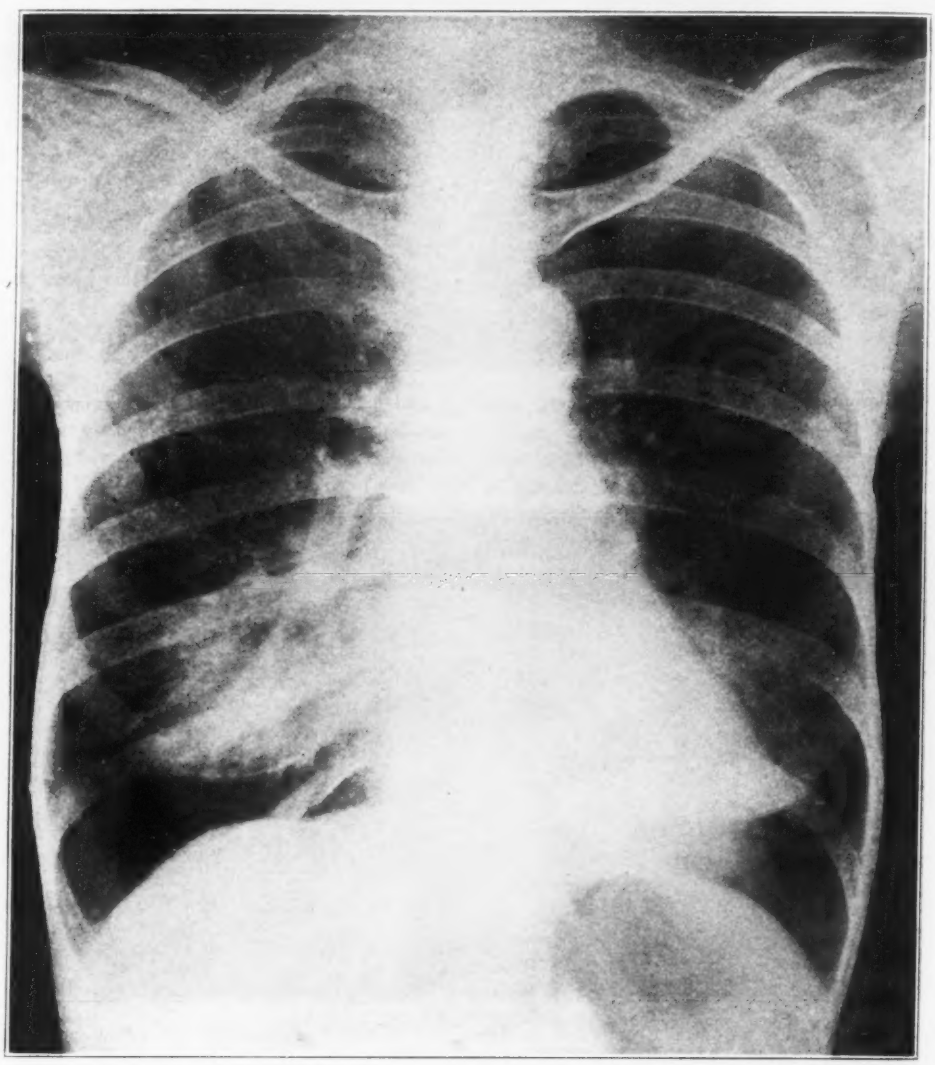

Fig. 4.—Moderate pulmonary fibrosis and calcification in the soft tissues overlying the thoracic cage.

Laboratory Data.—An electrocardiogram on Jan. 6, 1944 showed sinus fast rate, right axis deviation, low voltage throughout.

A roentgenogram of the chest on January 7 revealed deep fibrofascial thickening and calcification of soft tissues overlying the thoracic cage. This is more or less responsible for the general mottled appearance of both pulmonic fields. There is a moderate degree of peribroid nodulation at the hilus, with root branch fibrosis and moderate secondary productive changes. This is, however, devoid of definite etiologic characteristics other than probably interrelation or connection with the general tendency to deep subcutaneous fibrous changes and calcification. In addition to the central productive changes, there is also moderate interlobar septal thickening, seen mainly on the upper right side. The heart is inclined to the aortic type, with moderate left ventricular prominence. There is otherwise no actual increase in its transverse diameter. There is also a slight accentuation of the aortic arch.

An electroencephalogram on January 10 showed a moderate degree of diffuse electrocortical activity. The pattern suggests a widespread cerebral disturbance, most likely of a chronic nature. There is no evidence of a focal lesion.

A roentgenogram of the esophagus on January 10 showed the following significant features: moderate difficulty in deglutition; slight narrowing of the cardiac end of the esophagus but with no intrusional defect; calcified glandular deposits in the hilar nodes; osteoarthritic changes in the lower cervical portion of the spine; deep fibrofascial thickenings and calcifications of soft tissues over the thoracic cage.

A blood count on January 6 showed: erythrocytes 4,440,000; leukocytes, 12,200; hemoglobin content, 14 Gm. per hundred cubic centimeters (84 per cent); polymorphonuclear neutrophils, 41 per cent; eosinophils, 10 per cent; basophils, 1 per cent; lymphocytes, 36.5 per cent, and monocytes, 11.5 per cent.

Chemical examination of the blood on January 6, showed: total calcium, 11.2 mg.; inorganic phosphate, 4.8 mg.; phosphatase activity, 3.5 Bodansky units; urea nitrogen, 11.5 mg.; nonprotein nitrogen 33 mg.; urea nitrogen/nonprotein nitrogen, 35 per cent; chlorides as sodium chloride, 410 mg.; dextrose, 50 mg., and cholesterol, 145 mg.

The basal metabolic rate on January 6 was 28 per cent above the average normal. On January 7 it was +27 per cent.

Results of a vitamin C saturation test on January 10 (urinary excretion after injection of 1 Gm. of ascorbic acid intravenously) were: one and one-half hours, 186 mg. per 150 cc.; three and one-half hours, 214 mg. per 94 cc.; five hours, 400 mg. per 244 cc.

Routine examination of urine on January 6 revealed a specific gravity of 1.018 and a faint trace of protein. There were 1 or 2 white blood cells per high power field in addition to frequent bacteria and occasional urates.

The Wassermann reaction of the blood on January 6 was negative.

Examination of the urine for creatine and creatinine on January 11 was reported as follows:

	Excretion *		Normal,
	Gm./100 Cc.	Gm./24 Hr.	Gm./24 Hr.
Creatinine	0.14	0.9	1.0 - 1.5
Creatine	0.04	0.2	Less than 0.01
Total	0.18	1.1	

* Total amount of urine excreted in twenty-four hours, 614 cc.

Histologic Study.—A biopsy of the skin of the right thigh was performed, and the histologic report by Dr. Charles F. Sims was as follows:

"The surface of the epidermis is slightly irregular. It is covered in part by a mild loosely laminated horn layer. In part the granular layer is composed of two or three layers of flattened cells whereas in other areas it is absent. At several points, the interstitial lymphatic spaces are widened. In the center of the section the epidermis appears to be thinned.

"The vessels of the papillary and subpapillary zone are dilated, and the collagen surrounding them has undergone parenchymatous edema and in part granular degeneration. Some scattered chromatophores and eosinophils may be noted in the upper part of the corium; in the middle and deep layers of the corium there are irregular but well defined masses of collagen which stain a deeper pink than the surrounding collagen. The border of these affected masses as well as some of the fibers within the masses take a purplish stain. In these purplish areas the collagen has undergone fragmentation. The vessels of the deeper part of the corium are thickened and their lumen narrowed. There is a sparse cellular infiltration composed of small round and occasional wandering connective tissue cells present in the affected areas.

"The tissue stained with Weigert's stain for elastic tissue fibers reveals that throughout the upper portion of the corium the elastic tissue fibers have undergone fragmentation and at some points have disappeared."

Diagnosis.—The diagnosis was poikiloderma-like changes with calcinosis cutis.

Treatment and Subsequent Course.—The patient remained in the hospital long enough for completion of the aforementioned studies. On her discharge, topical medication and endocrine therapy were recommended to her family physician.

COMMENT

A Raynaud-like syndrome in association with generalized scleroderma associated with pigmentation and calcinosis cutis as herein illustrated was first described in 1910 by Thibierge and Weissenbach.[1] Since then other cases have been reported by these authors[2] as well as others.[3]

1. Thibierge, G., and Weissenbach, R.-J.: Une forme de concrétions calcaires sous-cutanées en relation avec la sclérodermie, Bull. et mém. Soc. méd. d. hôp. de Paris **30**:10-14, 1910.

2. Thibierge, G., and Weissenbach, R.-J.: Concrétions calcaires sous-cutanées et sclérodermine, Ann. de dermat. et syph. **2**:129-155, 1911; Concrétions calcaires sous-cutanées et sclérodermie et métabolisme du calcium, Paris méd. **16**:85-89, 1926. Weissenbach, R.-J.; Truchot, P.; Françon, F., and Laudat, M.: Rhumatisme chronique fibreux, sclérodermie et concrétions calcaires sous-cutanées. Étude radiologique et bio-chimique, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:837-847, 1931.

3. Hunter, W. K.: Sclerodermia, with Subcutaneous Calcareous Deposits, Glasgow M. J. **129**:241-250, 1913. Merklen, P.; Wolf, M., and Vallette, A.: Sclérodermie avec concrétions calcaires, Bull. Soc. franç. de dermat. et syph. **31**:120-126, 1924. Ormsby, O., and Ebert, M.: Raynaud's Syndrome (Sclerodactylia, Calcinosis and

(Footnotes continued on next page)

In 1932 Basch,[4] in a comphehensive thesis, reviewed the literature on this syndrome. The clinical picture is that of progressive scleroderma, with typical sclerodermatic facies, pigmentation and telangiectases. These may be preceded by or associated with vasomotor disturbances, such as paresthesias, acrocyanosis and angiospasm, or a Raynaud-like syndrome, usually of the upper extremities, resulting in sclerodactylia. As an end result the fingers assume the delicate supple features of those of an infant, and there are frequently associated calcareous concretions and ulcers. This syndrome occurs almost exclusively in women and is often associated with endocrine disturbances, especially ovarian hypofunction. In most cases the symptoms make their first appearance at the menopause, as was the case in this patient. Occasionally, however, there are prodromal symptoms such as arthralgia, fibrositis and rheumatic pains resulting in limitation of movement of joints.

Cases of generalized scleroderma with pigmentary changes, telangiectasia and superficial atrophy on the chest, abdomen and breasts, as shown by this patient, have been described as examples of scleropoikiloderma by Arndt, as reported by Jaffé.[5] H. Hoffmann[6] reported a case from J. Jadassohn's clinic; the patient suffered from generalized scleroderma associated with a Raynaud-like syndrome, calcinosis of the fingers and poikiloderma.

Internists are nowadays evincing more and more interest in scleroderma, particularly in the generalized variety. Banks[7] has suggested that there is a common denominator of such serious and at times rapidly fatal diseases as dermatomyositis, acute lupus erythematosus, periarteritis nodosa and generalized scleroderma.

My patient complained of dysphagia. Roentgenologic studies showed narrowing of the cardiac end of the esophagus. This narrowing has also been recorded by Ehrmann[8] and Ochsner.[9] There is further evidence of systemic involvement by the fact that roentgenograms showed moderate pulmonary fibrosis. This was first visualized by Murphy, Krainin and Gerson,[10] although it had previously been noted at autopsy by von Notthafft,[11] Matsui[12] and Kraus.[13] The abnormal electrocardiographic findings are in keeping with those reported by Weiss and associates[14] in "scleroderma heart disease." The electroencephalographic studies revealed a moderate degree of diffuse electrocortical activity, which Duryee[15] has found in over 80 per cent of cases of generalized scleroderma.

In generalized scleroderma telangiectases are frequently seen predominantly on the face, neck and chest, appearing as small angiomas and nevi aranei. The accompanying pigmentation, though diffuse, is usually confined to the sclerodermatous areas.

Most persons with the Thibierge-Weissenbach syndrome show localized calcinosis cutis, mainly affecting the fingers and joints. However, in my case one is dealing with a more generalized state of calcinosis cutis, calcium being deposited

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Changes), Arch. Dermat. & Syph. **12**:409-410 (Sept.) 1925. Pernet, J.: Ueber einen Fall von Sklerodermie und Hautverkalkung, Arch. f. Dermat. u. Syph. **152**: 337-343, 1926. Edeiken, L.: Scleroderma with Sclerodactylia, Am. J. Roentgenol. **22**:42-44, 1929. Granzow-Irrgang, D.: Sklerodermie plus Calcinose, Zentralbl. f. Haut- u. Geschlechtskr. **29**:608-609, 1929. Lortat-Jacob, L.; Fernet, P., and Bureau, Y.: Atrophie cutanée avec sclérodermie, mélanodermie et concrétions calcaires, Bull. Soc. franç. de dermat. et syph. **36**:256-260, 1929. Durham, R. H.: A Case of Scleroderma with Extensive Subcutaneous, Periarticular and Vascular Calcification, Ann. Clin. Med. **5**:679-691, 1927.

4. Basch, M.-C.: Le syndrome de Thibierge-Weissenbach; cóncretions calcaires des sclérodermies, Thesis, Paris, L. Arnette, 1932.

5. Jaffé, K.: Zwei Fälle von Sklero-Poikilodermie, Arch. f. Dermat. u. Syph. **159**:257-268, 1930.

6. Hoffmann, H.: Ueber circumscriptes, planes Myxödem mit Bemerkungen über Schleim und Kalk bei Poikilodermie und Sklerodermie, Arch. f. Dermat. u. Syph. **146**:89-104, 1923.

7. Banks, B. M.: Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? New England J. Med. **225**:433-441, 1941.

8. Ehrmann, S.: Ueber die Beziehung der Sklerodermie zu den autotoxischen Erythemen, Wien. med. Wchnschr. **53**:1156-1159, 1903.

9. Ochsner, A., and DeBakey, M.: Scleroderma: Surgical Considerations, New Orleans M. & J. **92**: 24-30, 1939.

10. Murphy, J. R.; Krainin, P., and Gerson, M. J.: Scleroderma with Pulmonary Fibrosis, J. A. M. A. **116**:499-501 (Feb. 8) 1941.

11. von Notthafft, A. F.: Neure Arbeiten und Ansichten über Sklerodermie, Zentralbl. f. allg. Path. u. path. Anat. **9**:870-960, 1898.

12. Matsui, S.: Ueber die Pathologie und Pathogenese von Scleroderma universalis, Mitt. a. d. med. Fak. d. k. Univ. zu Tokyo **31**:55-116, 1924.

13. Kraus, E. J.: Zur Pathogenese der diffusen Sklerodermie, Virchows Arch. f. path. Anat. **253**:710-734, 1924.

14. Weiss, S.; Stead, E. A., Jr.; Warren, J. V., and Bailey, O. T.: Scleroderma Heart Disease, with a Consideration of Certain Other Visceral Manifestations of Scleroderma, Arch. Int. Med. **71**:749-776 (June) 1943.

15. Duryee, C. A.: Personal communication to the author.

er the knuckles, elbows and knees as well as the chin, neck, wall of the chest, shoulders, illas, lumbar and iliac crest regions and antero-teral aspects of the thighs. The ulcerations condary to the calcium deposits and the pain ere responsible for the limitation of movement d muscular wasting. The generalized wasting as in part due to inanition as a result of dys-agia.

An interesting feature of this case is the pres-ce of acrodermatitis chronica atrophicans of is rare but has been reported by Herxheimer,[16] Kingsbury,[17] Kanoky and Sutton,[18] Gottheil,[19] Trimble,[20] Pautrier [21] and Jessner and Loewenstamm [22] among others. Much has been written on the development of sclerodermatous changes on the legs in cases of primary idiopathic atrophy, and these are now regarded as part of the picture of acrodermatitis chronica atrophicans. The unusual feature is the simultaneous appearance of generalized scleroderma with definite poikiloderma-like changes, calcinosis and acroderma-

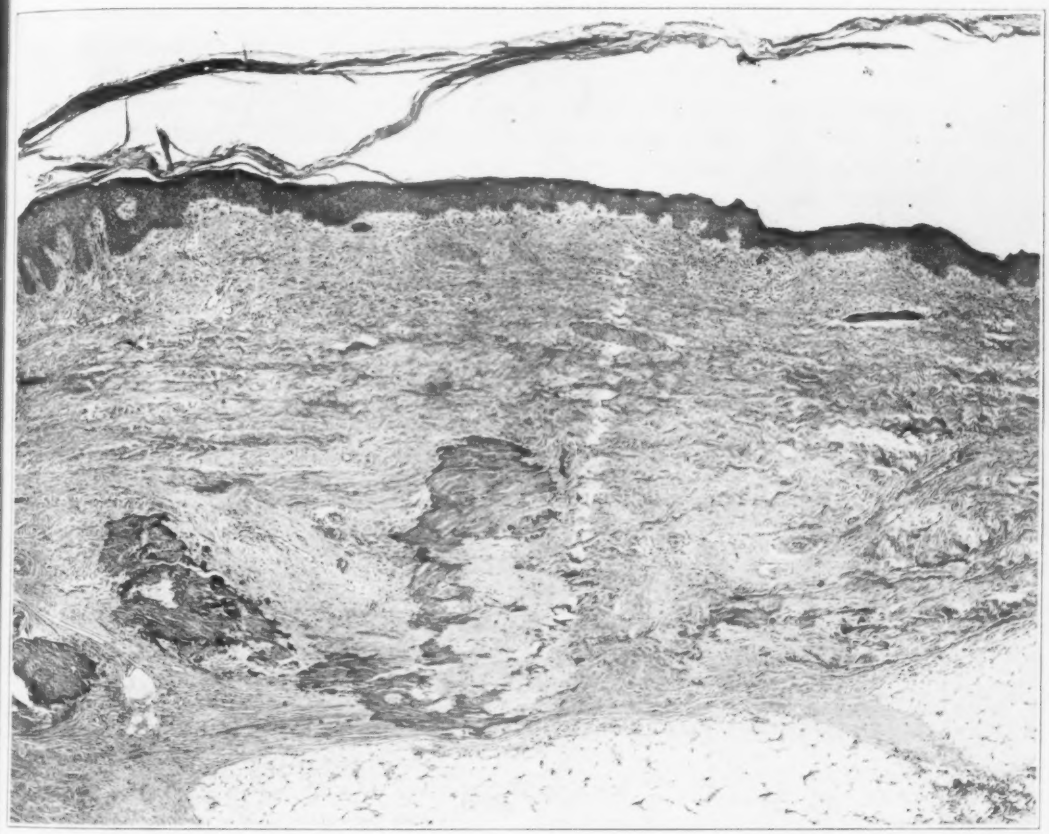

Fig. 5.—Note the flattening of the epidermis in the center of the section and the dark irregular areas of calcinosis in the deep portion of the cutis. Low power magnification; hematoxylin and eosin.

he dorsa of the hands and involving the extensor surface of the elbows. The coexistence of sclero-derma and acrodermatitis chronica atrophicans titis chronica atrophicans, the last confined to the dorsa of the hands and the extensor surface of the elbows.

16. Herxheimer, C.: Further Observations on Acro-dermatitis Chronica Atrophicans, J. Cutan. & Ven. Dis. **23**:241-245, 1905.

17. Kingsbury, J.: A Case of Acrodermatitis Chronica Atrophicans with Co-Existing Scleroderma, J. Cutan. & Ven. Dis. **25**:414-416, 1907.

18. Kanoky, J. P., and Sutton, R. L.: A Comparative Study of Acrodermatitis Chronica Atrophicans and Diffuse Scleroderma, with Associated Morphoea Atrophica, J. Cutan. & Ven. Dis. **27**:556-566, 1909.

19. Gottheil, W. S.: Acrodermatitis Chronica Atrophicans with Scleroderma, J. Cutan. & Ven. Dis. **32**:586-587, 1914.

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21. Pautrier, L.-M.: Les rapports de la dermatite chronique atrophante, de l'anétodermie et de la sclérodermie. L'étude des troubles du métabolisme du tissu conjonctif, Bull. Soc. franç. de dermat. et syph. **6**:973-978, 1929.

(Footnotes continued on next page)

Calcium was observed in acrodermatitis chronica atrophicans by M. Jessner [23] as early as 1921. The author did not link this with a possible disturbance of the calcium metabolism, which linkage is apparent in the case here reviewed.

The association of scleroderma, scleropoikiloderma, calcinosis cutis and acrodermatitis chronica atrophicans raises the question as to the interrelationship of this whole group of diseases the pathogenesis of which is probably related to endocrine disturbances.

CONCLUSIONS

In the case herein reported generalized progressive scleroderma developed in a woman at the menopause. The scleroderma was associated with a Raynaud-like syndrome, poikiloderma-like changes and generalized calcinosis cutis.

This case is an example of the combination of a sclerotic disease and atrophoderma: scleroderma with acrodermatitis chronica atrophicans.

Birk's Building.

22. Jessner, M., and Loewenstamm, A.: Bericht über 66 Fälle von Acrodermatitis chronica atrophicans, Dermat. Wchnschr. **79**:1169-1171, 1924.

23. Jessner, M.: Zur Kenntnis der Akrodermatitis chronica atrophicans, Arch. f. Dermat. u. Syph. **134**: 478-487, 1921.

EFFECT OF FOLLICULOID HORMONES ON ABNORMAL SKIN

FURTHER OBSERVATIONS OF THE EFFECT OF ESTRADIOL ON THE SKIN OF MICE OF THE RHINO, HAIRLESS AND NAKED STRAINS

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In an earlier communication I described the main histologic characteristics of the structure of the skin of the so-called rhino mouse. I also showed that chronic local application of estradiol to the skin causes increased keratinization of the abnormal hair follicles and accentuates the resemblance of this congenitally abnormal skin to that characteristic of ichthyosis follicularis.[1]

In the course of continued experiments on this subject it was found that young animals of the rhino strain respond to folliculoids[2] in an entirely different manner, inasmuch as in them a generalized cutaneous and subcutaneous edema develops. It was suspected that the reason for this was that their skin is not protected by the thick layer of keratinized epithelium which covers the surface of the old rhino mouse. In order to test this assumption, I repeated the experiment with so-called hairless mice. In this strain the skin is comparatively fine even during adult life and is not as intensely keratinized as in rhino animals. Mice of this hairless strain always respond with edema formation. It is probable that the abnormal condition of the skin sensitizes it to the edema-producing action of the folliculoids. The absence of hair in itself does not explain this abnormal sensitivity, as is shown by the following observations. Mice of a third, the so-called naked, strain differ from the hairless mice in that they lose their hair only in patches (fig. 1) and the structure of the skin remains essentially normal. All the observations which my colleagues and I have made up to the present time indicate that the hair-free areas of the skin of naked mice do not respond with edema formation, nor does the skin of normal shaved mice react in this manner. It is probable that the lack of abnormal response in mice of the naked strain as well as in shaved normal mice is due to the fact that the structure of their skin is nearly normal and has not acquired the characteristics of that of the hairless or young rhino mice which are necessary for the abnormal response to folliculoids.

In the present communication I shall report on a typical experiment of this series which will illustrate the course of this abnormal response of the skin to treatment with estradiol.

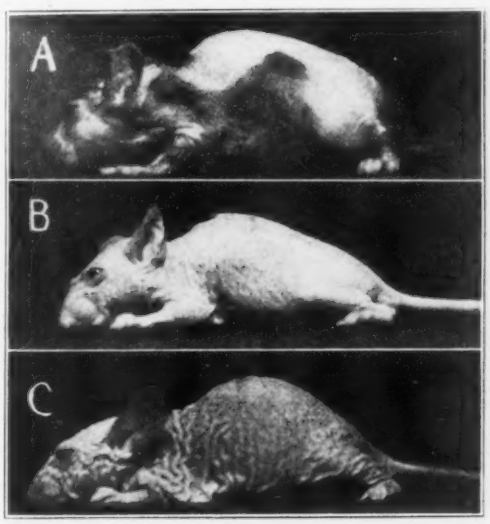

Fig. 1.—*A*, a mouse of the so-called naked strain. Note that some areas of the skin retain their hair. Histologically the skin of such animals is essentially normal. *B*, a mouse of the so-called hairless strain. The entire body surface is practically free of hair, and even the hair follicles are degenerate. All layers of the skin are atrophic. *C*, a mouse of the so-called rhino strain. In this adult animal the skin is thick, wrinkly and heavily keratinized. Young animals of this strain are, however, almost indistinguishable from the young of the hairless strain.

Ten male and 10 female hairless mice weighing between 14 and 24 Gm. were subdivided into two equal groups, each consisting of 5 males and 5 females. All animals were fed on "Purina dog chow" (meat meal, dried skim milk, wheat germ, barley malt, dried beet pulp, corn grits, cereal feed from corn and wheat, dried raisins, soy

From the Department of Anatomy, McGill University.

1. Selye, H.: Effect of Estradiol Locally Applied to Abnormal Skin, Arch. Dermat. & Syph. **48**:188 (Aug.) 1943.

2. The term "folliculoid" is used to designate substances having an activity resembling that of the ovarian follicles (Selye, H.: Pharmacological Classification of Steroid Hormones, Nature, London **148**:85, 1941).

bean oil meal, molasses, riboflavin supplement, dried brewers' yeast, vitamin A and D feeding oils, 1 per cent steamed bone meal and 1 per cent iodized salt) and water both before and during this experiment. The 10 mice of the first group were used as controls, and their skin was merely treated once daily with ordinary peanut oil, which was gently applied over the back by means of a cotton pad. The mice of the second group were similarly treated with peanut oil in which

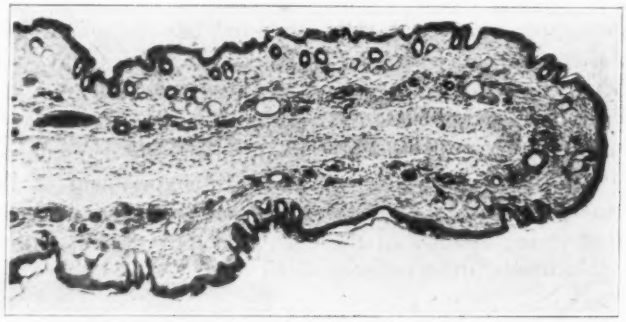

Fig. 2.—Histologic section through a fold of skin (lumbar region) of an untreated hairless mouse.

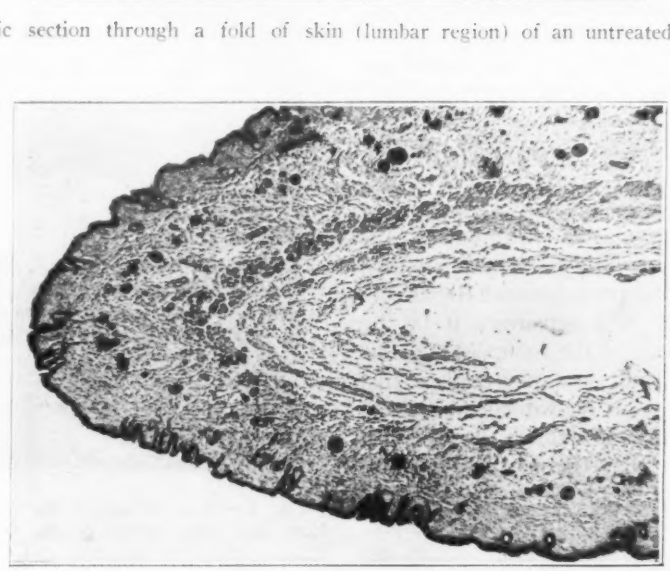

Fig. 3.—Histologic section through a fold of skin of an estradiol-treated hairless mouse. The specimen was taken from the same region and photographed under the same magnification as that in figure 2. Note the pronounced thickening of the entire chorium due to accumulation of hyaline mucoid material.

250 micrograms of estradiol per cubic centimeter was dissolved. In this manner the applied solvent and the daily handling were identical in the two groups and the only difference was the presence of estradiol in the solution used for treatment of the experimental animals. While the skin of the control animals did not change its macroscopic appearance, that of the experimental animals became swollen and translucent at about the fifth day of treatment. A few days later the entire surface of the back exhibited a pronounced nonpitting edema in all animals of the estradiol-treated group. At this time a small sample of the skin was removed for histologic examination and it became obvious that the edema extended far into the subcutaneous layers, down to the fasciae of the muscles of the back.

Histologic examination of the specimens of skin showed that all layers of the cutis and subcutis were greatly swollen with edema. Indeed the connective tissue in these layers resembled that seen in the sex skin of monkeys during estrus,[3] in capons' combs after administration of testoid substances or in endometrial moles[4] pro-

3. (*a*) Bachman, C.; Collip, J. B., and Selye, H.: The Effects of Prolonged Oestriol Administration upon the Sex Skin of Macaca Mulatta, Proc. Roy. Soc. London, s.B **117**:16, 1935; (*b*) Further Studies of Sex Skin Reactions in Macaca Mulatta, Proc. Soc. Exper. Biol. & Med. **33**:549, 1936.

4. Selye, H., and Friedman, S.: On the Production of Endometrial Moles with Steroid Hormones, Am. J. Cancer **38**:558, 1940. Selye, H.; Harlow, C., and McKeown, T.: The Endometrial Mole, Proc. Soc. Exper. Biol. & Med. **32**:1253, 1935.

duced under the influence of folliculoid hormones. This mucoid connective tissue is characterized by the presence in the intracellular spaces of a definitely tingible, though light, hyaline material which probably represents a type of mucin rather than ordinary edema transudate. The facts that the edema does not pit and that after discontinuation of treatment usually five to ten days or more elapse before it disappears make it highly unlikely that one is dealing merely with a result of transitory circulatory disturbances.

It has always been puzzling to the histologist why connective tissue in certain areas of the skin closely associated with the sex organs—for instance, in the sex skin of monkeys, the comb of cocks, the clitoris and penis and other organs—should respond to sex hormones differently from similar cells in other cutaneous regions. Earlier transplantation experiments of my colleagues and me [3b] showed that such sensitive cutaneous areas retain their responsiveness to hormones after transplantation into a hormone-insensitive area of skin while insensitive skin remains irresponsive even after transplantation into the genital region. The experiments reported in this communication indicate that under certain circumstances the entire cutaneous surface may acquire such a specific sensitivity to hormones.

It is tempting to correlate our experimental findings with the cutaneous changes which tend to occur in connection with certain phases of the menstrual cycle in women, since the latter also appear to be of hormonal origin. However, morphologically the resemblance of our experimental lesion with the cutaneous changes typical of scleredema adultorum (Buschke) is perhaps even more striking. The literature on the latter disease has been summarized in the excellent reviews of Epstein [5] and Sweitzer and Laymon.[6]

From the etiologic point of view the only fact so far established is that in almost every case it follows some acute infection or other type of sudden exposure to stress. There is no reason to believe that such an acute damaging condition would increase the production of folliculoid hormones, but definite evidence is not available that the folliculoids are the only hormonal compounds capable of eliciting this change. It is well known that exposure to sudden stress, such as occurs in acute infections, elicits an "alarm reaction" with great increase in the hormone production of the adrenal cortex.[7] Since the adrenal glands produce steroids chemically and physiologically related to the folliculoids, it appears possible that the pathogenesis of scleredema adultorum is in some manner related to that of the experimental condition described in this communication.

SUMMARY

In the so-called hairless mouse, whose skin is affected by a congenital anomaly, local application of estradiol to the surface of the skin elicits a generalized nonpitting cutaneous edema. On histologic examination the structure of the affected areas resembles that of the mucous connective tissue in the sex skin of estrous monkeys or in the comb of cocks. There is a possible relationship between this experimental lesion and scleredema adultorum (Buschke).

The expenses of this investigation were defrayed through a grant received from the International Cancer Research Foundation.

Dr. A. G. Steinberg and F. C. Fraser, of McGill University, supplied the rhino, naked and hairless mice, and Dr. Erwin Schwenk, of the Schering Corporation, of Bloomfield, N. J., donated the estradiol necessary for these experiments.

5. Epstein, N. N.: Scleredema Adultorum (Buschke), J. A. M. A. **99**:820 (Sept. 3) 1932.

6. Sweitzer, S. E., and Laymon, C. W.: Scleredema Adultorum (Buschke), Arch. Dermat. & Syph. **37**:420 (March) 1938.

7. Selye, H.: The Alarm Reaction, in Piersol, G. M., and Bortz, E. L.: Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, 1940, vol. 15, p. 15.

PREPARATION OF MATERIAL FOR LABORATORY DIAGNOSIS OF SOME TROPICAL DISEASES OF THE SKIN

LEON GOLDMAN, M.D.

CINCINNATI

Since most dermatologists have had or will have only an occasional opportunity to observe some tropical cutaneous diseases, it is important to secure as adequate confirmatory laboratory diagnosis as possible. In tropical medicine the laboratory plays an important role. Often standard texts do not include the practical details for the laboratory diagnosis.

Some general considerations may be given at first. Since parasites may often be few, perseverance and persistency are needed in the search for them. The casual glance or the examination of only a small portion of the slide preparation is entirely inadequate for the conclusion that the result of a test is negative. A systematic search of the slide should be made; multiple examinations should be done, and examinations should be repeated at varying intervals if indicated. When slides are used, it is important that they be clean; otherwise the preparation may not remain on the slide, or confusing artefacts may occur. Moreover, the examination of preparations should not be left to the inexperienced laboratory technician or physician. Permanent mounts can often be made and sent for diagnosis, and smears may be fixed well on the slide, wrapped in tissue paper and sent to a laboratory with an experienced staff for good staining and diagnosis. Some specific points will be considered in relationship to the specific disease.

There is little clinical interest for the dermatologist in the cutaneous picture of malaria. Malarial pigmentation of the skin may occasionally suggest staining of the skin from bile pigments or systemic drugs, such as picrates and aniline dyes. Moreover, discoloration from quinacrine hydrochloride confuses the cutaneous picture and may occasionally produce a band-like discoloration of the scleras (Peña Chavarría). In the tropics it is difficult for the inexperienced clinician to differentiate discoloration of the skin due to malaria from that following administration of quinacrine hydrochloride and that from the all too common anemias secondary to intestinal parasitism. Eruptions due to quinine may occur in malarial patients, but they will not be common unless use of quinine becomes more widespread. If malarial pigmentation of the skin is suspected in the absence of a history of malaria, the thick blood smear for the presence and identification of the parasites should be used; the thin smear is less satisfactory.

In the tropics some cases of pruritus ani are due to intestinal parasites. Oxyuriasis, or pin worm infection, may also occur in adults, and since the parasites lay their eggs on the skin, the search for these eggs must be made by the rubbing of swabs over the skin about the anal orifice rather than by the search through the formed stool element. The perianal area must not be cleaned, washed or rubbed before the smears are taken. Cellophane swabs should be used, and they should be rubbed well into the folds about the anal orifice; then the cellophane strip should be smoothed out on a slide, covered with a cover clip and examined. Sutliff has shown that occasionally ova of other parasites may be recognized in this fashion.

If rare amebiasis cutis is suspected in an ulceration, either perianally, about a draining liver sinus or about a colostomy area, fresh preparations are necessary. It is important to remember that such cutaneous pictures may be due to secondary infection, usually coccic or with Bacillus coli, or to the irritating effect of discharge rather than to the amebas.

If filariasis is suspected, one must remember that search for the filariae, especially in cases of Wuchereria bancrofti infections, may be disappointing. Biopsy in cases of Calabar swellings is reported to be satisfactory and is extremely valuable in the diagnosis of onchocercomas of onchorerciasis but is not of much value for infections with W. bancrofti. Here, puncture of a lymph node may be done (inguinal node preferred?), or the blood may be examined in the late evening, between 11:00 p. m. and 1:00 a. m. For the diagnosis of filaremia, a venipuncture is

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This work was done under grant from the John and Mary R. Markle Foundation to the Committee on the Teaching of Tropical Medicine of the Association of American Medical Colleges, Henry E. Meleney, Chairman.

ade (femoral vein preferred?) and a number slides prepared by allowing a thick drop to ttle on each slide and to dry without air bub- es. At the same time a concentration test may started. After the slides are made, for the oncentration test 1 cc. of blood and 9 cc. of olution of formaldehyde are put into a test tube nd allowed to stand over night. If the smears re negative, then the concentration test is fol- wed through. The mixture of blood and olution of formaldehyde is centrifuged, and the ediment is pipetted off, carefully smeared and tained. Instead of formaldehyde, acetic cid may be used and the sediment ashed repeatedly with distilled water and ecentrifuged, or a mixture of acetic acid nd Giemsa stain may be used, so that the sedi- ent is stained. However, in infections with W. bancrofti, the diagnosis, especially in the late tages, will be made by the clinical picture and he history of exposure rather than by any posi- ve results of laboratory tests. For the diag- osis of onchocercoma or onchodermatitis (Díaz) small piece of skin of the ear may be clipped ff and the actively motile microfilariae demon- trated in the specimen in saline solution. Fix- tion with 10 per cent solution of formaldehyde ill secure a permanent mount. Drying of the pecimen in plasma and then staining with iemsa stain will also make permanent mounts. hese sections from the ear may be made irre- pective of the location of the onchocercoma or ven in complete absence of onchocercoma. As rule, the number of microfilariae depends on he distance of biopsy from the onchocercoma. he diagnosis of onchocercoma may be made by queezing the excised bit of tissue and seeing the xtrusion of the adult filarial form. Under the issection microscope this worm may be teased ut and examined. The biopsy of an onchocer- oma may show the adult form, the ova and the icrofilariae or in old lesions, eosinophilic ab- ess, fibrosis and calcification. In the biopsy f an area of onchodermatitis whether in its rysipelatous phase, *erisipela de la costa* or *mal morado*, or with scaling, lichenoid and hyper- igmented cutaneous changes, the microfilariae re found usually in the dermis. In the ocular ype of onchocerciasis, the microfilariae are re- orted to be seen with the slit lamp also. For he diagnosis of loaiasis (Calabar swellings) he microfilariae are reported to be found in the lood during the day, and the same technic as or the demonstration of W. bancrofti may be sed. It is reported also that in persons with oaiasis the adult forms may be found in the skin nd in the conjunctivas. Bozicevich has de- eloped intradermal and serologic tests for on- chocerciasis. Eosinophilia is found with filari- asis, especially with onchocerciasis, for which a figure of 83 per cent has been reported.

For the laboratory diagnosis of leprosy, ma- terial for smears is taken from inside the nose and from the skin, and the smears are stained with Ziehl-Neelsen or acid fuchsin technics. If little material is obtained from the nose or the smear is negative for lepra bacilli, the patient may be given potassium iodide for a brief period and then the smears repeated. The preparations from the skin may be taken from intact skin or from a leproma. The skin is squeezed between a Kelly clamp (rubber tubing may be used on the sides of the clamps to prevent slipping), and the lymph fluid from the split skin is taken di- rectly on a slide, smeared out and stained. The upper outer aspect of the arm or forearm may be used. If a scalpel is used to abrade the skin, un- less care is taken, too much bleeding may be caused and the specimen will be more difficult to examine. Biopsies with acid-fast stains may be made of the lepromas, thickened nerve trunks, etc.

Considerable care must be taken for the labor- atory diagnosis of cutaneous leishmaniasis. An early lesion should be chosen and preferably one not infected secondarily, since many of the exten- sive ulcerative types are due usually to secondary infection. The material for smear or culture should be taken from the edge and under the edge of the lesion or from the indurated portion about the edge or scraped from the surface of clean granulation tissue. Smears may be stained with Leishman's stain and culture made on a special blood medium, such as the N. N. N. medium. If cultures are made on Senekjie's medium, exact details regarding temperature, etc., must be maintained. If the subject has any suspicious visceral involvement, even though this may be thought to have no relationship to the clinical picture, examination for leishmaniasis should be made wherever practicable. This may include puncture of the spleen usually or even of the liver (where the technic is known) and sternal puncture. Intradermal and serologic tests are also available. Occasionally the difficult pro- cedure of xerodiagnosis may be employed, with designated species of Phlebotomus.

Cutaneous myiasis is common in certain tropi- cal areas, and the lesions on first inspection may simulate pyogenic infections of the skin. The opening may be very small and may appear to be a small pus cap, especially if there is no move- ment of the parasite. With a fine forceps the top may be removed and the parasite extracted. It is well also to attempt to determine the parasite concerned rather than to discard the specimen.

If the lesion is old and there is considerable pus, the parasite may be necrotic and suspected bits of this may be fixed and sections cut for examination.

For the search for the organism of pinta, Treponema carateum, before any therapy is used, the edge of the spot of the skin may be prepared in the same manner as in the search for the lepra bacillus. The small clear drops of lymph secured are taken up on a cover slip and dark field examination made. Tissue secured may also be stained with Levaditi or Warthin-Starry stain. As is well known, a positive serologic reaction of the blood may be found in almost 100 per cent of cases.

Because of the confusion with other forms of treponematoses and the positive serologic reactions of the blood, for instance in malaria and leprosy, the clinical diagnosis of cutaneous syphilis in the tropics must be made with caution, especially in the phase of the syphilids and the cutaneous gummas. Dark field examinations of the syphilids or of material from puncture of a lymph node may be of help for the diagnosis of syphilids, and negative results of examinations of the gummas for some of the ordinary agents responsible for granulomas in areas where the person resides may be of some aid in the diagnosis of gummas. At the present time therapeutic tests, even with penicillin, are not of great practical value in the differential diagnosis.

The clinical aspects of the case will be of greater value in the differential diagnosis of yaws from syphilis. Treponema pertenue cannot be differentiated morphologically from Treponema pallidum. A biopsy specimen showing severe degrees of acanthosis may be of some value with acanthotic types but will not help with the papular or erythematosquamous types.

The same precautions for the collection of specimens of suspected mycotic granulomas apply for the tropics as elsewhere. Especially in the late lesions material as free of secondary infection as possible should be used for culture, identification and animal inoculation studies.

The parasite Tunga penetrans can be recognized easily when picked out, and portions, if necrotic or ruptured, may be fixed and examined. I have had no experience with the laboratory diagnosis of cercarial dermatitis in schistosomiasis. Depending on the type of schistosomiasis the ova are reported to be found in urine or feces. Cercarial dermatitis (urticarial forms) of the Great Lakes area of the United States has been studied, and parasites are not found, since the skin here is bitten but not penetrated.

For the diagnosis of the tropical ulcer syndrome, the bacteriology of the untreated ulcer, preferably the ulcer after treatment with saline packs, must be studied. Fusospirillar or diphtheritic types cannot be diagnosed clinically with certainty. It has been noted that at times even the ordinary stasis syndrome ulcer of persons in the upper age group is included in that vague classification of "tropical ulcer."

Many other details for the aid in the diagnosis of tropical dermatoses may be found in standard texts. Only those practical aspects which have been found to be of value to the nonexperienced dermatologist are reviewed here.

DYSTROPHIA UNGUIUM MEDIANA CANALIFORMIS

REPORT OF A CASE

LESTER P. FOWLE, M.D.
LEWISBURG, PA.
AND
LIEUTENANT RICHTER H. WIGGALL (MC), U.S.N.

In 1928, J. Heller [1] described an unusual deformity of the nails characterized by the development of a canal in the body of the nail plate running from the free edge to the root, which he termed "dystrophia unguium mediana canaliformis." No etiologic factor has been found.

The following case is presented mainly because the nails cleared after removal of dental foci of infection. This fact may offer a possible clue to the causation. We believe this to be the first case described in the literature as occurring in North America.

REPORT OF CASE

Mrs. T. A., a white, 23 year old, married American housewife, reported for examination on May 27, 1942, stating that she had first noted trouble with her nails a year before. Since then all her nails had been involved at one time or another. There was no history of familial diseases of the nails or of allergy. The nails of the thumbs were first involved. Central longitudinal ridges first appeared, and later tunnels (canals) developed from the tip of the nail to the matrix. These later fissured and gave the nail a "split" appearance. The deformities appeared while she was having severe pains of a neuralgic type in the lumbar region together with sharp pains down her arm. She had been nervous for some time and in the past six months had felt rather tired. There was no history of trauma to the nails.

At the time of examination the left third, fourth and fifth nails had cleared spontaneously.

General physical examination revealed essentially normal conditions except for the nails and two dead teeth. The nails were thin and tended to be spoon shaped or had concavities on either side of the central tunnel, which on the right index finger had opened near the tip, to give the nail a split appearance. There was moderate onychorrhexis. The nail of the right index finger had a definite tunnel into which a fine wire could be inserted almost to the matrix; the nails of the middle and ring fingers of the right hand and that of the index finger of the left hand had tunnels, but into them no wire could be inserted because the ends were not open.

The toe nails, chiefly those of the great toes, were thickened, friable and undermined.

The patient stated that she had been able to stick a toothpick partially into the tunnels at other times and that the great toe nails had had tunnels.

Laboratory studies showed the hemoglobin content, the red and white blood cell counts and the differential distribution to be normal. Histologic studies were not made. A culture of scrapings from the finger nails on Saboraud's medium revealed a penicillium, while that of scrapings from the toe nails grew cryptococci. These organisms were not considered of diagnostic significance because of their universal prevalence.

The patient was referred for dental consultation and was given roentgen irradiation (75 r) of the left thumb nail for trial. She was also given ¼ teaspoon (2 Gm.) of washed sulfur twice a day.

Dystrophia unguium mediana canaliformis.

She was seen eighteen days later. She had not improved, but she had just had three carious teeth removed that had had "pus sacs" on the roots. She had taken only one dose of sulfur because it "upset her stomach." No further roengten ray treatment was given.

A year and a half later without further treatment the nails were entirely clear. She stated that they began to improve two months after the extraction. The pains in her back and arm likewise disappeared, and she has not been troubled since.

SUMMARY

In a patient with dystrophia unguium mediana canaliformis the nails returned to normal after removal of dental foci of infection. No treatment to date has been universally successful.

We believe that foci of infection may be etiologic factors. It is probable that in some

From the Dr. S. Lewis Ziegler Memorial Infirmary, Bucknell University.

1. Heller, J.: Dermat. Ztschr. **51**:416-419 (Jan.) 1928.

cases dystrophia unguium mediana canaliformis is not recognized because of the failure to attempt to demonstrate a canal. Unless the physician is familiar with the disease, it will be unclassified or given an incorrect diagnosis.

We suggest that this disease should be suspected wherever there are fissures of the nails. Our patient had fissures extending about half the length of the nail plate which ended in tunnels continuing on toward the matrix. We believe the fissures are caused by breaking down of the roof of the tunnel or canal.

We suspect that the disease is much more common than the sparse reports in the literature would indicate.[2]

We wish to point out that in the case reported some of the nails had cleared spontaneously before the teeth were extracted.

2. Wucherpfenning, V.: Dermat. Ztschr. **54**:98 (Aug.) 1928. Pardo-Castello, V.: Diseases of the Nails, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1941, p. 96. Costa, O. G.: Median Canal-Like Dystrophy of the Nail: Report of a Case, Arch. Dermat. & Syph. **47**:406-407 (March) 1943. Ledo, E.: Ann. de dermat. et syph. **10**:765 (July) 1929.

Clinical Notes

ROSACEA IN TWINS

THOMAS S. SAUNDERS, M.D., PORTLAND, ORE.

While summer prurigo,[1] alopecia areata,[2] psoriasis,[3] ichthyosis hystrix,[4] eczema,[5] von Recklinghausen's disease[6] and lichen planus have been reported in twins, I have not seen any record of the occurrence of rosacea in twins. Hence, I report the following case.

REPORT OF A CASE

M. E. aged 43, a female stenographer, complained of an eruption on the face of one year's duration. Examination (Feb. 22, 1944) showed a fairly extensive eruption of tiny acneform superficial erythematous papules around the margins of the face. Diascopic pressure completely expressed all color from the lesions. No history of ingestion of drugs could be elicited. The diagnosis of rosacea was made. The patient volunteered the information that her twin sister (said to be identical) had had a similar eruption four months before. At that time they had been separated, my patient living in Washington, D. C., and the twin living in Portland, Ore. Examination of the twin showed milder but typical rosacea. The application of a sulfur-resorcinol paste resulted in prompt improvement in both patients.

1020 South West Taylor Street.

1. Parkhurst, H. J.: Summer Prurigo of Hutchinson in Twins, Arch. Dermat. & Syph. **14**:625 (Nov.) 1926.

2. Turnacliff, D. D.: Alopecia Areata in Twins, Arch. Dermat. & Syph. **24**:1122 (Dec.) 1931.

3. Vohwinkel, K. H.: Psoriasis in Twins, Dermat. Wchnschr. **94**:340 (March 5) 1932; abstracted, Arch. Dermat. & Syph. **26**:343 (Aug.) 1932. Mayr, J.: Heredity in Psoriasis Vulgaris, Dermat. Wchnschr. **106**:569 (May 21) 1938; abstracted, ibid. **40**:610 (Oct.) 1939.

4. Gross, P.: Ichthyosis Hystrix in a Twin, Arch. Dermat. & Syph. **35**:520 (March) 1937.

5. Sharlit, H.: Coincidence and Dermatoses, Arch. Dermat. & Syph. **36**:1084 (Nov.) 1937.

6. Loftis, E. L.: Recklinghausen's Disease in Identical Twins, Arch. Dermat & Syph. **42**:657 (Oct.) 1940.

SUPPRESSION OF SYPHILIS BY PENICILLIN THERAPY OF GONORRHEA

LIEUTENANT COMMANDER HUGH E. HAILEY (MC), U.S.N.R.

Injection of penicillin is the choice method of therapy for gonorrhea, whether sensitive or resistant to sulfonamide compounds. Too frequently gonorrhea is only one of two or more venereal diseases contracted from a single exposure. Because of the beneficial effect of penicillin on syphilis, thorough and repeated clinical and laboratory studies to rule out syphilis should be pursued before one administers this drug for gonorrhea, as was learned from the following case.

REPORT OF A CASE

A. C., a white man, aged 22, found a small sore on his penis March 15, 1944. Three weeks prior to this time he had an illicit sexual affair. On the mucous surface of the prepuce there were two small denuded, granular, rather firm erosions with the tendency to bleed on moderate manipulation. The entire prepuce was edematous and partially phimotic. The inguinal lymph nodes were firm, palpable and nontender. From March 15 to March 27, results of daily dark field examinations were negative; however, on March 23 the Gram stain revealed the presence of gonococci. Sulfathiazole was given routinely but administration was discontinued on March 30 because of an urticarial rash and failure of the drug to influence the urethral discharge.

After twelve negative results of dark field eexminations and five negative Kahn reactions, 100,000 units of penicillin was administered in five doses at three hour intervals intramuscularly on April 3. The urethral discharge had ceased by the next day. The ulcers of the prepuce were entirely healed on April 18, and the Kahn reaction of the blood was negative.

On May 1 there was a recurrence of the ulcers and moderate edema of the prepuce. Two Kahn tests of the blood on succeeding days elicited positive reactions. Dark field examinations gave negative results. Antisyphilitic treatment rapidly reduced the penile lesions to normal. The Kahn reaction was negative on June 5.

COMMENT

The dosage of penicillin was sufficient to cure the gonorrhea but was enough only to obscure the syphilis. From the rapid response to mapharsen and a bismuth preparation in this case, it appears that penicillin does not contribute to fixed positive Kahn reactions nor does it make syphilis resistant to arsenical and heavy metal therapy.

Obituaries

FREDERICK H. DILLINGHAM, M.D.
1857 - 1944

Dr. Frederick H. Dillingham died in New York on Aug. 30, 1944, at the age of 87. He had served on the staff of the New York Polyclinic Hospital for fifty-nine years, until March of this year, when ill health compelled his retirement. From 1915 to the present year, he served as one of the professors of dermatology and, in spite of his advanced years, was the medical executive officer of the institution from 1928 to this year.

Dr. Dillingham was born in Bangor, Maine, his earliest paternal ancestor settling in Lynn, Mass., in 1630. On his mother's side, he was descended from John Alden.

Dr. Dillingham obtained the degree of B.A. in 1877 and of M.A. in 1880 from Bowdoin College, Brunswick, Maine. He received the degree of M.D. from Columbia University in 1882 and later interned at St. Francis Hospital, New York. He was connected with the Department of Health of New York city from 1882 to 1903. He was consulting dermatologist to St. Francis' Hospital and St. Joseph's Hospital, New York, and St. John's Riverside Hospital, Yonkers.

He was a Fellow of the American Medi Association and of the New York Academy Medicine. He also served as secretary of t section of hygiene of the latter institution fr 1892 to 1894.

The affectionate regard of his associates the New York Polyclinic Medical School a Hospital was shown by the fact that his pho graph appeared as the frontispiece in a rec history of the institution.

News and Comment

AMERICAN BOARD OF DERMATOLOG AND SYPHILOLOGY

The next examination of the American Board Dermatology and Syphilology will be held in New Yo city, June 8 and 9, 1945.

The written portion of the examination will be giv to B candidates in various cities throughout the Unit States on April 23, 1945. Applications close on Mar 12, 1945.

Application blanks and further information may b obtained from the secretary, Dr. George M. Lew 66 East Sixty-Sixth Street, New York 21.

Correspondence

CONTACT ECZEMA DUE TO NAIL POLISH

To the Editor:—In our article "Contact Eczema Due to Nail Polish" (ARCH. DERMAT. & SYPH. **49**:183 [March] 1944) we stated that we had found that one or more solvents elicited a positive reaction in 20 of 30 patients sensitive to nail polish. The solvents used in our study were M.H.P. Gum Solvent, Proprietory Solvent and No. 10 Solvent (benzine). The company which supplied them refused to divulge the chemical nature of these materials.

Dr. Harry Keil called our attention to the fact that toluene sulfonamide formaldehyde resin has been used in straw hat lacquer under the name of M.H.P. Gum Solvent. It appears that M.H.P. Gum Solvent is not a real solvent in the ordinary application of this term, and this name seems to be a commercial way of disguising its composition. M.H.P. Gum Solvent is in reality a synthetic resin, toluene sulfonamide formaldehyde, the same substance which Keil and Van Dyck found to be the offending agent in 25 of 26 cases of nail polish dermatitis (ARCH. DERMAT. & SYPH. **50**:39 [July] 1944). This was confirmed by the Lorr Laboratory in response to our inquiry about the nature of th "solvent."

In the light of these facts we should like to pres our data in revised form. It may now be noted that the 30 patients tested 6 reacted to toluene sulfonami formaldehyde resin alone and 9 additional persons re sponded to this substance and in addition also to on of both of the aforementioned solvents (Proprietory an benzine). Five patients gave positive reactions to th Proprietory Solvent and No. 10 Solvent but did no react to the toluene sulfonamide formaldehyde resi The reactions in all cases were read as 2 and 3 plu Six patients did not give a positive reaction to any o the substances that we tested with. The synthetic resi apparently is not the sole cause of dermatitis due t nail polish. From our observations it seems that th toluene sulfonamide formaldehyde resin is the sensitiz ing agent in about 50 per cent of the cases. The nitro cellulose base, natural resins, solvents, plasticizers and dyes act as sensitizers in the remaining cases.

WILLIAM L. DOBES, M.D., Atlanta, Ga.
PHILIP H. NIPPERT,
LIEUTENANT, MC-V(S), U.S.N.R.

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

STUDIES IN SYPHILIS: I. REVIEW OF THE INCIDENCE OF SYPHILIS IN AUTOPSIES ON ADULTS. PAUL D. ROSAHN and BERNARD BLACK-SCHAFFER, Arch. Int. Med. **72**:78 (July) 1943.

Rosahn and Black-Schaffer intend to review 5,300 autopsies performed at Yale since 1917. As the first step, they present a critical review of the available literature on the incidence of syphilitic infection in persons aged 20 or over as revealed by postmortem studies. They point out the wide divergences in the incidence reported in various studies (2.6 to 29.5 per cent). Even when only reports from the United States are considered, they may be grouped in two sets, those reporting an average frequency of 4.4 per cent and those reporting an average of 19 per cent. Rosahn and Black-Schaffer point out that the divergence cannot be ascribed to differences in race, sex, age or social and economic status of the populations studied, but rather to the use of different diagnostic criteria, both gross and microscopic. The authors plan a detailed study of these criteria.

CARCINOMA WHICH SIMULATES SARCOMA—A STUDY OF ONE HUNDRED AND TEN SPECIMENS FROM VARIOUS SITES. SAMUEL MCLEOD BROOKS, Arch. Path. **36**: 144 (Aug.) 1943.

Brooks pointed out that any large number of cancers includes a certain small proportion of obviously highly malignant ones whose origin cannot be easily differentiated as epithelial or mesenchymal. Several groups of such tumors, most of which had been classified as carcinomas, were studied in order to establish a clearer basis for the determination of possible epithelial origin. Twenty-eight cases of carcinoma arising from the epithelium of the skin or lip formed the largest group, and these were the most intensively studied. For inclusion in this group the usual criterion was that a lesion should be a diffuse cancerous growth of spindle-shaped cells. Among the 28 patients there were 7 who lived five years or more after an operation had been performed.

Brooks gave particular attention to asymmetric mitotic figures in the basal layers of the epithelium and to disintegration of the basement membrane. In the tumors with sarcomatous appearance, the fusiform cells usually seemed to arise in the basal layer of the epidermis but Brooks noted 1 case in which they arose in the upper layers; this would seem to indicate that the change is due to a property intrinsic in the tumor cell, rather than in the environment. Special stains for collagen and reticulum were found useful to indicate the presence or absence of a basement membrane. No significant differences in the amount or arrangement of the reticulum or collagen between sarcomas and sarcoma-like carcinomas were noted. Brooks pointed out that melanomas frequently are composed entirely of spindle-shaped cells and could well be confused with carcinomas of the type under consideration.

The factors determining the assumption of a diffuse sarcomatous appearance by carcinoma cells did not become evident during the study. Most authors have stated that this change is due to the characteristics of the invaded tissue, but Brooks concluded that probably the fusiform shape is due to an intrinsic characteristic of the tumor cell itself, though previous trauma and irradiation which have also been suggested as causes, were possibly slightly more frequent in the cases of sarcoma-like carcinoma of the skin and the lip than in cases of typical carcinoma of these tissues.

PIGMENTED PAPILLOMA OF SKIN. ROBERT A. FOX, Arch. Path. **36**:195 (Aug.) 1943.

Fox reports a small group of cases of pigmented tumor such as that described by Bloch as "benign pigmented epithelioma" and by others as a type of nevus. These brown, round or oval lesions had a polypoid button shape and a warty appearance. The microscopic structure was that of a pigmented, papillary tumor made up of nests of closely packed epithelial cells.

In describing this type of tumor, Fox rejects the term "epithelioma" because of the confusion resulting from the "benign" versus "malignant" connotations. The term "intraepidermal epithelial nevus" is rejected by him because he would reserve the word "nevus" for those tumors which contain nevus cells. He urges that dermatologists and pathologists completely discard the word "mole" in order to avoid confusion. The name "pigmented papilloma of the skin" is suggested as one which is compatible with the morphologic and histologic features of the growth.

LYNCH, St. Paul.

ZINC PEROXIDE—A NEW DRUG FOR RAPIDLY CURING THE SWOLLEN PREPUCE. GORDON G. ALLISON, J. A. M. A. **124**:774 (March 18) 1944.

At the Atlanta City Venereal Disease Clinic zinc peroxide was used in treatment of over 400 cases, particularly of venereal diseases producing ulcerative lesions of the male genitals, namely syphilis, chancroid, granuloma inguinale and fusospirochetosis.

A piece of rubber tubing is attached to a powder blower or insufflator. Zinc peroxide powder is placed in a glass receptacle. The open end of the rubber tube is placed in the opening of the foreskin, and the skin is firmly held against the rubber tube. The powder is forcefully blown about the glans penis and under the foreskin. The patient is instructed not to wash or irrigate himself but to return in two or three days for another treatment.

The secretions are immediately lessened; the edema subsides; the induration and swelling disappear; the mucosa and skin become pliant, and ofttimes on the next visit the foreskin can be retracted. The hazard of gangrene and the need for dorsal slits are eliminated.

ACTINOMYCOSIS OF THE SUBCUTANEOUS TISSUE OF THE FOREARM SECONDARY TO A HUMAN BITE. R. A. ROBINSON, J. A. M. A. **124**:1049 (April 8) 1944.

Robinson reports a case of actinomycosis of the subcutaneous tissue of the forearm secondary to a human

bite. A persistent inflammatory lesion followed the bite, which stubbornly resisted all treatment for over two years, when the ray fungus was found in the granulation tissue. After the abscess was opened, a dressing of sulfanilamide crystals and zinc peroxide paste was applied to the wound without packing almost every day postoperatively for three weeks. The wound completely healed in four weeks.

A Rapid Treatment for Scabies. Albert H. Slepyan, J. A. M. A. **124**:1127 (April 15) 1944.

Slepyan treated 189 persons with scabies with benzyl benzoate and followed them for more than fourteen days. No recurrences were noted. Two patients concurrently infected with pediculosis pubis were also cured of their pediculosis by the scabicide.

Cause and Treatment of Furunculosis. Philip B. Price, J. A. M. A. **124**:1189 (April 22) 1944.

Price believes that a local spread of infection is sufficient to account not only for the features of furunculosis but for its characteristic chronicity. It is his opinion that the usual mode of spread of infection in furunculosis is by discharges, sweat, bathing and friction, which smear the pathogenic organisms over the surface of the skin.

He recommends that an attempt be made to sterilize the skin of the whole contaminated region. Healthy skin can be thoroughly degermed with exactly 70 per cent ethyl alcohol. Price washes the involved area for from twenty to thirty minutes with the alcohol. The optimum time to employ this treatment is in the interval between the healing of the last furuncle and the onset of the next one. Eleven patients with furunculosis so treated had prompt and permanent relief.

Recurrent Bullous Eruption of the Feet and Hands (Weber-Cockayna): Localized Epidermolysis Bullosa. Morris Waisman, J. A. M. A. **124**:1247 (April 29) 1944.

Two instances of an unusual hereditary blistering dermatosis of the feet and hands are reported. An additional atypical case, an example of "acquired" localized epidermolysis bullosa, which does not possess heredofamilial characteristics, is also described.

In epidermolysis bullosa an inherent vulnerability of the skin leads to the formation of blebs over a part subjected to mechanical trauma. The abnormality is localized to a great extent, the feet manifesting the lesions preponderantly and in many cases even exclusively. One of the cases reported is unique because of strict limitation of the lesions to the fifth toes, onset in the third decade of life and absence of other familial cases.

All 3 patients were soldiers, and the strenuous physical demands of military life may have been conducive to activation of a latent blistering tendency. Diagnosis is aided by the family history, onset in childhood and relationship to excessive walking or manual work.

Occupational Contact Dermatitis of Aircraft Workers. A. F. Hall, J. A. M. A. **125**:179 (May 20) 1944.

Hall observed 370 cases of industrial dermatitis, constituting 63.8 per cent of all cases of dermatitis seen. Zinc chromate primer was responsible for the eruption in 132 cases, duralumin in 10 cases and alminum in 4 cases. After an employee has become sensitized to zinc chromate primer, even the most indirect contact may be sufficient to initiate a flare-up of the dermatitis. Of the 132 persons with dermatitis due to contact with the primer, 90 were sensitive to the zinc chromate pigment only. The average length of exposure before the appearance of the eruption was seven months. The distribution of the lesions of the skin is characteristic. In order of frequency the sites are the radial and flexor aspects of the wrists, the dorsal aspects of the proximal portions of the thumbs, the volar and ulnar aspects of the forearms, the dorsal aspects of the hands and fingers and occasionally the ankles at the "short sock level." In Negro workers sensitive to zinc chromate pigment the eyelids, the sides and front of the neck and the cubital fossae are invariably affected. No involvement of eyelids was encountered in white workers unless sensitivity to resins was also demonstrated.

Seventeen employees with dermatitis due to contact with the primer were found to be sensitive to one or more of the resin ingredients of the primer but not to the zinc chromate pigment. The average duration of exposure before the onset of symptoms is only slightly less than the average quoted for the group sensitive to zinc chromate pigment. The eyelids were affected in all cases, and the sides of the upper two thirds of the neck and the cubital fossae in the great majority.

Nineteen employees proved sensitive to one or more of the resins as well as to the zinc chromate pigment. The clinical picture presented by the patients of this group was exactly what one would expect to obtain by superimposing one of the types of dermatitis described on the other.

No evidence of development of tolerance to either the zinc chromate or the resins, once an employee is sensitized, has been observed.

In duralumin dermatitis some aspect of the forearms was involved in all cases. The eruption is characterized by scattered fine pale pink papules, usually excoriated. The excoriations are of the fine pinpoint, sanguineous crusted type frequently associated with scabies.

In all 4 persons with dermatitis due to contact with aluminum the flexor surfaces of the forearms and wrists were affected. The lesions themselves tend to be wheal-like and suggest insect bites but are without central puncta. In general, the lesions are more erythematous than those from other contacts, particularly immediately after work, but they may disappear entirely within twenty-four hours away from work.

Henschel, Denver.

The Source of the Allergic Activity of House Dust. Marion T. Davidson, J. Allergy **14**:24 (March) 1943.

The author feels that there is little reason to look beyond the self-evident substances which are present in houses and expect to find some unknown substance.

"House dust is composed of cotton, flax, jute, wool, silk, six or more animal hairs, three or more feathers, glue, kapok, orris root, pyrethrum, and tobacco."

In the discussion of the paper, Alan G. Cozart suggests that the antigen in house dust may be a product of the deterioration of cellulose (cotton and kapok).

Hoyer, Cincinnati. [Am. J. Dis. Child.]

HISTAMINASE IN THE TREATMENT OF ALLERGY IN CHILDREN. M. MURRAY PESHKIN, HOWARD G. RAPAPORT, WILLIAM MESSER, IRVING FEUER, ADELE SICULAR and ARTHUR BERGER, J. Pediat. **22**:426 (April) 1943.

Forty-eight children, ranging in age from 3 to 16 years, who had previously been studied and treated for allergic conditions, were each given 50 units of histaminase (torantil) over a period averaging nine weeks. The allergic manifestations included asthma, hay fever, vasomotor rhinitis, urticaria, migraine and angioneurotic edema. The drug proved to be ineffective not only as a prophylactic agent but as a therapeutic adjunct. In fact, results were poorer than those which one obtains with other nonspecific types of therapy for allergy. The use of histaminase is based on the assumption that histamine is a factor producing smooth muscle spasm and localized edema, manifestations of anaphylaxis and allergy. The authors state that, since this theory has never definitely been proved, the value of a counteracting histaminase is questionable.

STETTENBENZ, Buffalo. [AM. J. DIS. CHILD.]

TOXICITY AND EFFICACY OF PENICILLIN. HARRY J. ROBINSON, J. Pharmacol. & Exper. Therap. **77**:70 (Jan.) 1943.

Studies were made on mice with penicillin, a relatively impure derivative of Penicillin notatum. The toxic dose of penicillin was about sixty-four times the therapeutic dose as determined by subcutaneous injection. "On the basis of weight, penicillin appears to be more effective than sulfanilamide and its derivatives in streptococcal, pneumococcal and staphylococcal infections in mice."

PILCHER, Cleveland. [AM. J. DIS. CHILD.]

VARICELLA FOLLOWING EXPOSURE TO HERPES ZOSTER. JOSEPH GARLAND, New England J. Med. **228**:336 (March 18) 1943.

The mother of 2 children, a daughter aged 8 years and a son aged 6, first noticed soreness of the left side of her throat on January 23. By January 28 pain and swelling of the left side of her face had developed, and on January 30 a typical eruption of herpes zoster appeared on this area. She had had varicella in childhood. Fourteen days after her first symptoms had appeared, the son showed the scattered papules of an eruption that became well defined varicella twenty-four hours later, and on the following day the husband and the daughter broke out with typical, moderately severe chickenpox. No exposure to chickenpox had occurred for any of the 3. The daughter had been confined to the house with a cold since the beginning of her mother's illness, and no attacks of the disease had occurred in the small school group of which the son was a member.

GENGENBACH, Denver. [AM. J. DIS. CHILD.]

ACTINOMYCOSIS TREATED WITH SULPHAPYRIDINE. R. W. BILLINGTON, Brit. M. J. **1**:326 (March 4) 1944.

In a proved case of actinomycosis in which roentgen ray therapy and iodides failed to keep the disease under control, sulfapyridine was administered, with excellent results.

CRANIAL-NERVE PALSIES WITH HERPES FOLLOWING GENERAL ANAESTHESIA. J. H. HUMPHREY and MARGARET MCCLELLAND, Brit. M. J. **1**:339 (March 4) 1944.

Thirteen cases of palsy of cranial nerves following general anesthesia are reported. The disease was associated with labial herpes in 9 cases. The nerves involved were mainly the fifth and seventh, but the third, fourth, sixth, tenth and twelfth were involved in some cases.

No anesthetic drug was common to all cases, but there was evidence to suggest that chemical reaction between soda lime and trichloroethylene in the system was responsible for the toxic effect.

Antibodies against herpes were found in the serums of all patients. It was suggested that until further investigations have been made trichloroethylene should not be used when there is any possibility of its coming into contact with soda lime.

SHAW, Chattanooga, Tenn.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

DAVID BLOOM, M.D., *Chairman*

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Dec. 4, 1943

An Intradermal Reaction as an Aid in the Diagnosis of Granuloma Inguinale. Presented by BORRIS A. KORNBLITH, M.D.

A tissue antigen was prepared from an acute lesion of granuloma inguinale of six weeks' duration in which Donovan bodies were especially numerous and easily demonstrable on smear with Wright's stain (fig. 1 *A*). The extensive distribution of Donovan bodies in the resected specimen was easily demonstrated in paraffin tissue section stained by the Giemsa method.

The test material was prepared in the following manner: a fair-sized piece of tissue was removed and triturated in a small amount of isotonic solution of sodium chloride in a sterile mortar. The triturated material was diluted so that it would be possible to aspirate it through a 26 gage needle. It was then bottled and heated at 60 C. for two hours on one day and left in the refrigerator overnight. It was heated at 60 C. for one hour on the following day. After this procedure, the material was tested for sterility both aerobically and anaerobically and was found sterile. Smears showed no organisms or Donovan bodies. It did show amorphous pink-staining debris. It must be noted that this material was not filtered. It is fairly certain that the tissue was originally contaminated with organisms present on the skin, staphylococci and streptococci. These organisms did not interfere with the quality or effectiveness of the antigen. The manner of preparation is similar to that used in making Frei antigen for lymphogranuloma venereum.

A series of 19 patients with proved granuloma inguinale and another series of control subjects were given intradermal injections of 0.1 cc. of this test material, and the results were observed in forty-eight hours. A negative result showed no evidence of reaction in the skin. A positive result consisted of a tender nodule and infiltration about 5 to 8 mm. in diameter surrounded by an erythematous halo of varying size.

The explanation of the "false negative" or "false positive" reactions requires further study.

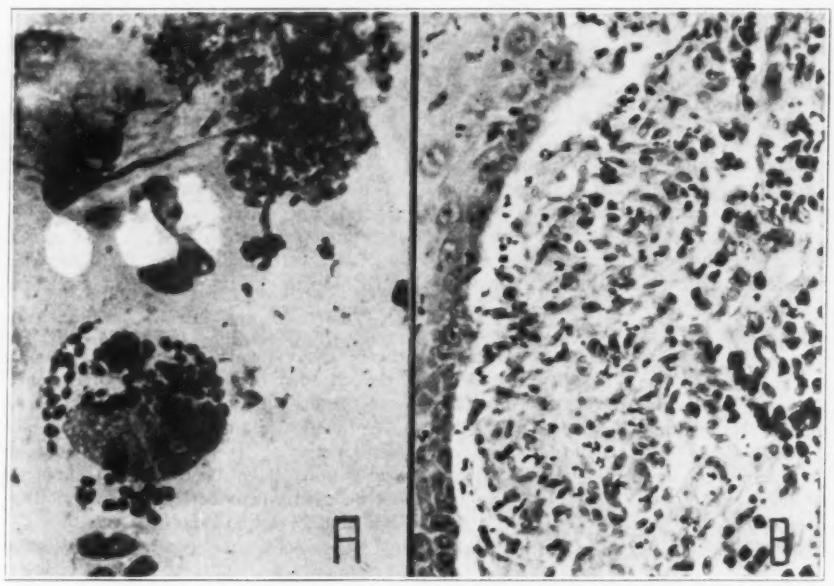

Fig. 1.—*A*, Donovan bodies in a monocyte and breaking out of a monocyte to appear free on smear. From a six week old lesion of granuloma inguinale; Wright's stain. *B*, section of tissue from an acute lesion of granuloma inguinale, showing epithelioid nodules with leukocytic infiltration. Hematoxylin and eosin.

Histopathology of the Intradermal Reaction for Granuloma Inguinale.—An oval portion of skin was excised containing a positive intradermal reaction three days after injection of the test material into a patient with definitely proved granuloma inguinale. Sections were stained with hematoxylin and eosin and Giemsa stain. The microscopic study was made by Dr. Sadao Otani. The essential picture was that of a diffuse epithelioid cell reaction. Epithelioid cells were present diffusely throughout the corium. They assumed a characteristic pattern and were arranged in spheres of varying sizes. The characteristic feature was that of an epithelioid nodule or sphere. The periphery consisted of more compactly arranged layers of epithelioid cells, while the centers were made up of a more loosely arranged interlacing network of epithelioid cells. Within these clusters, there were a moderate number of lymphocytes and plasma cells. There was no evidence of acute inflammation. The reaction was conspicuous by the

sence of polymorphonuclear leukocytes. There was evidence of necrosis (fig. 2*A*). Some giant cells were present (fig. 2*B*). Donovan bodies were not found in the intradermal reaction.

A review of the sections of tissue taken from an acute lesion of granuloma inguinale containing numerous Donovan bodies in the monocytes revealed similar epithelioid structures in places. These structures were modified by the presence of acute inflammatory changes as a result of secondary infection. The epithelioid structure was obscured by exudate consisting of polymorphonuclear leukocytes, lymphocytes and plasma cells (fig. 1*B*); giant cells and fresh granulation tissue were likewise present.

It is important to observe that the descriptions of the histopathology of granuloma inguinale up to the present are consistent with a description of nonspecific inflammation due to secondary infection with contaminating organisms which accompany these open lesions. The histologic reaction as seen in the intradermal tests is uncontaminated and gave a lead to a similar picture in the original granuloma inguinale lesions. There is thus present a histopathologic correlation between the actual lesions and the confirmatory intradermal reaction of granuloma inguinale.

An analogous correlation was shown to exist in lymphogranuloma venereum between the histology of the Frei reaction and the histopathology of the lymph nodes (Kornblith, B. A.: Observations on Lymphogranuloma Venereum, *Surg., Gynec. & Obst.* **63**:99, 1936).

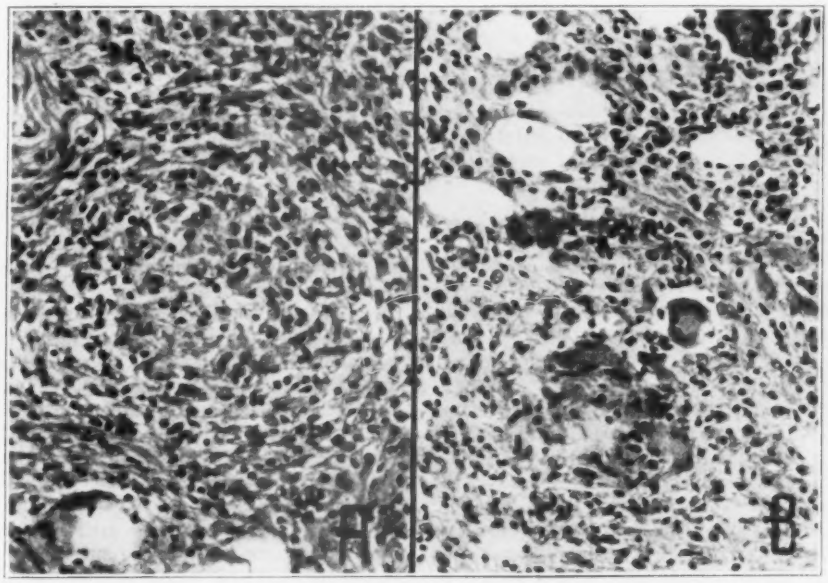

Fig. 2.—Intradermal reaction of granuloma inguinale, showing (*A*) characteristic epithelioid sphere with many lymphocytes and (*B*) giant cells in a mesh of epithelioid cells.

Granuloma Inguinale of the Vaginal Wall. Presented by DR. BORRIS A. KORNBLITH.

M. M., a Negress aged 31, is presented from the Central Clinic, Bureau of Social Hygiene, Department of Health, of the City of New York. On admission to the clinic she complained of a soreness in the perineum of three weeks' duration. She had been treated for syphilis in May 1939; she received adequate treatment and was considered to have got maximum benefit from her therapy. In February 1943 she was treated for gonorrhea, and in September 1943 she again suffered from a gonococcic infection of the cervix. This infection cleared under sulfathiazole therapy.

A superficial, fleshy, friable, bleeding ulceration 3 cm. in diameter is present in the vaginal wall on the left side at a distance of 3 cm. from the hymen. There is another similar ulceration at the fourchet. The cervix is clean. The uterus is in midposition and not enlarged.

Donovan bodies were found on smear from both lesions. An intradermal reaction to the injection of granuloma inguinale antigen was positive. Smears for Ducrey bacilli were negative. The Wassermann reaction of the blood has remained persistently 4 plus since 1939. The patient is now receiving antimony and potassium tartrate intravenously twice a week.

NOTE.—This patient is a contact of N. D., a Negro, who shows on his genitalia active lesions of granuloma inguinale of one year's duration.

Granuloma Inguinale. Presented by DR. BORRIS A. KORNBLITH.

N. D., a Negro aged 34, is presented from the Central Clinic, Bureau of Social Hygiene, Department of Health, of the City of New York, complaining of ulcerations in both groins and a flat ulceration on the prepuce, of one year's duration. A serpiginous ulceration is present in the right groin just above the inguinal ligament. The ulceration has a fleshy appearance, is relatively clean looking, does not have a foul odor and is slightly raised above the surface of the skin. It measures 6 cm. in length and 2 cm. in width. A separate lesion is present on the dorsal aspect of the prepuce. This lesion measures about 3 cm. in diameter and has a similar fleshy appearance. In the left inguinal region a healed scar is present.

Donovan bodies were found in smears from both lesions. An intradermal reaction to granuloma inguinale

antigen was positive. Dark field examinations did not reveal spirochetes, and smears were negative for Ducrey bacilli. The Wassermann reaction of the blood, the Frei reaction and the reaction to Ducrey vaccine were all negative.

The patient was given antimony and potassium tartrate 5 cc. of a 1 per cent solution, intravenously twice a week over a period of two months, for a total of seventeen injections. The lesions promptly underwent involution. It is planned to continue treatment for about nine months. After the lesion is completely healed, he will receive one injection of 5 cc. of 1 per cent solution of antimony and potassium tartrate weekly to prevent recurrence.

NOTE.—This patient is a contact of M. M., a Negress aged 31, who shows a lesion of granuloma inguinale in the vaginal wall.

DISCUSSION OF THE TEST FOR AND THE CASES OF GRANULOMA INGUINALE

DR. NATHAN SOBEL: Dr. Kornblith was kind enough to show me all these tests and controls, and they were as stated. Wright's stain was used at the Central Clinic to demonstrate Donovan bodies.

DR. WILLIAM CURTH: I believe that Dr. Kornblith is to be congratulated on showing 1 of the few proved partner cases of granuloma inguinale. It is strange that the lesions of granuloma inguinale and chancroid are not seen more often inside the vagina. I should like to ask Dr. Kornblith if he has prepared only one antigen for his test.

DR. PECK: I wish to congratulate Dr. Kornblith. The majority of the investigators who examine lesions for Donovan bodies try to look for one form. While I am entirely in agreement that what has been accepted as typical Donovan bodies represents one phase of the organism, there are also other phases which are true Donovan bodies. The histologic picture may differ, as far as the organism is concerned, from that obtained from a smear. It is not uncommon to find groups of organisms which resemble diplococci or even staphylococci in smears. I interpreted these as developmental forms of the organism. One of the characteristic pictures that the organism produces in cells which can be beautifully illustrated in the smears has rarely been described. I refer to the large histiocytes which have peculiar "cap" formations over the nucleus.

There has been some discussion about a virus being the etiologic agent of granuloma inguinale. This seems not substantiated by the histologic sections, since the typical cells in granuloma inguinale with their organisms cannot be differentiated from rhinoscleroma, and there is no doubt in any one's mind that the latter disease is due to a bacillus.

DR. BORRIS A. KORNBLITH: There has been a remark about the tuberculoid appearance of these lesions and their resemblance to those of lymphogranuloma venereum. It must be pointed out that until recently the histologic description of lesions of the venereal diseases has been that of nonspecific inflammation. The reason is that the lesions are all infectious granulomas as a result of inoculations with specific agents. The lesions are essentially granulomas and thus far have depended on the isolation of the individual causative agents for their specific identification. However, further histologic study has led to the finding of characteristic lesions in lymphogranuloma: a microabscess with a peripheral zone of epithelioid cells with a center containing leukocytes, lymphocytes and plasma cells and areas of necrosis. The Frei reaction was likewise shown to have a specific histopathologic structure. I had the privilege of presenting this subject before the New York Pathological Society and at the New York Academy of Medicine in November 1935 (Kornblith, B. A., Transactions of the New York Pathological Society, *Arch. Path.* **21**:252, 1936; Observations on Lymphogranuloma Venereum, *Surg., Gynec. & Obst.* **63**:99, 1936).

The histopathologic structure of the reaction to intradermal injection of tissue from granuloma inguinale shown tonight presents a characteristic picture, the epithelioid sphere. Similar characteristic histologic structures were likewise found in the biopsy of an active lesion of granuloma inguinale. It is thus evident that the finer pathologic details of these two diseases are definitely different and they may thus be identified by their characteristic histologic structure. It is obviously an open subject, and it would be well to have the observations reported tonight confirmed when more sections are studied.

A question has been raised as to the authenticity of the Donovan bodies shown. That question was answered by Dr. Peck. There is no doubt whatever that the pictures shown are those of Donovan bodies. Perhaps they were rather better than those usually seen. I may refer to the complete work of Dr. Robert B. Greenblatt, of Augusta, Ga. (Experimental and Clinical Granuloma Inguinale, *J. A. M. A.* **113**:1105 [Sept. 16] 1939), to confirm these findings. In our experience at the Central Clinic, Miss Frances Kaplan was able to demonstrate Donovan bodies in 24 of 27 consecutive cases of suspected granuloma inguinale. I may mention, too, that lymph nodes may likewise exhibit Donovan bodies in monocytes. Thus one has a complete clinical and pathologic correlation of the intradermal reaction, the local lesion and the involvement of lymph nodes.

Another question resolves itself into whether or not syphilitic persons show an intradermal reaction in granuloma inguinale different from that of nonsyphilitic persons. I may state that a positive reaction occurred when granuloma inguinale was present and that it was not influenced by the presence of syphilis. Four of 19 patients with granuloma inguinale had positive Wassermann reactions of the blood. Negative control reactions were likewise obtained on patients with positive Wassermann reactions.

Dr. Curth asked about the preparation of one or more antigens. Thus far only one antigen has been prepared from a patient who showed numerous Donovan bodies in the tissue. It would prove of great value to produce a number of different antigens. The question of false negative reactions might possibly be elucidated by testing with different antigens, since a single antigen may not elicit positive results in all cases of proved granuloma inguinale.

Dr. Peck brought up an interesting point about finding cells so overloaded with Donovan bodies that they appear to make a complete cover around the monocyte. My colleagues and I have also observed that. The mechanism appears to be as follows: One Donovan body may invade the cell and begin to multiply and then fill it completely, until the cell bursts. At this point the Donovan bodies can be found both intracellularly and free. It is apparently not difficult to find Donovan bodies if they are looked for diligently.

We have found the following technic useful for making smears: A small piece of tissue to be examined

removed from the lesion either by scraping or by excision. Smears are made by crushing this tissue. Donovan bodies are best found in the tissue exudate which is expressed from the crushing. The Wright stain has been adequate for smears.

Granuloma Inguinale; Syphilis. Presented by DR. NATHAN SOBEL.

C. E., a Negro aged 34, is presented from the Central Clinic, Bureau of Social Hygiene, Department of Health, of the City of New York, complaining of a painful swelling of the right groin and an ulceration of the shaft of the penis, of one week's duration. He was treated for syphilis thirteen years ago at Bellevue Hospital, where he received thirteen intravenous injections of arsphenamine and fifteen intramuscular injections of a bismuth preparation.

There is a pronounced adenitis in the right inguinal region. The inguinal lymph nodes are diffusely enlarged to the size of a plum and are tender. They are not broken down. On the shaft of the penis there is a small, flat, superficial ulceration, 5 mm. in diameter. The surface of the lesion is relatively clean. It is surrounded by an area of brawny edema which measures 4 cm. in diameter and 1 cm. in thickness.

A smear from the penile lesion revealed numerous Donovan bodies, and the intradermal reaction to the injection of granuloma inguinale antigen was positive. The Wassermann reaction of the blood two months before the patient's admission to the clinic was negative. Two Wassermann tests made on this admission elicited 4 plus reactions. Results of a Frei test and a Ducrey vaccine test were negative. Dark field examination and puncture of a lymph node for Treponema pallidum did not reveal their presence.

The patient is now receiving 5 cc. of a 1 per cent solution of antimony and potassium tartrate twice a week intravenously.

DISCUSSION

DR. DAVID BLOOM: This patient probably has a mixed infection, for the bubo has the features of lymphogranuloma venereum. The Frei test should be repeated several times, for the reaction may be delayed.

DR. MAURICE J. COSTELLO: At Bellevue Hospital a fair number of cases of granuloma inguinale are observed. In general, when a single lesion occurs on the shaft of the penis, I think it is frequently called the initial lesion of syphilis or chancroid. In the presence of a single lesion of the penis, one should also suspect the possibility of granuloma inguinale. I think the other members of the staff at Bellevue Hospital will agree with that statement, because this has been our experience.

DR. NATHAN SOBEL: The Frei test was repeated, but it was too early to read it this evening. There is no question that granuloma inguinale can be confused clinically with lymphogranuloma venereum or syphilis. I should like to call particular attention to the fact that in the past with single nodular lesions on the penis the diagnosis of granuloma inguinale was frequently missed because an intensive search was not made. I have given antimony and potassium tartrate empirically to some of these patients as a therapeutic test, and the lesions have cleared.

NOTE.—The second Frei test elicited a negative reaction on Dec. 31, 1943. Aspiration of the inguinal lymph node failed to show Donovan bodies or Treponema pallidum.

Granuloma Inguinale with Lymphedema of Prepuce and Penis Due to Scarring. Presented by DR. TIMOTHY J. RIORDAN.

T. L., a Negro aged 25, was admitted to Bellevue Hospital because of discomfort, swelling and ulceration of the penis. No definite history could be obtained from the patient, but from his statements the probable history seems as follows: In 1937 or 1938 he contracted gonorrhea. Simultaneously, or soon after, a sore developed on the penis which healed completely after several injections (arsenic and bismuth preparations) into an arm and a hip. Treatment was continued for about six months. About three years later new sores appeared on the penis, for which he received a number of intravenous injections (antimony and potassium tartrate?), but these sores never healed completely and the organ seemed to get more and more swollen.

Examination reveals several irregular, granulating ulcers on the glans penis and prepuce associated with pronounced distortion of the glans, scarring and considerable edema of the prepuce and shaft of the penis.

Examinations of the blood and urine gave essentially negative results. The Wassermann and Kahn reactions of the blood were 4 plus. The Frei test elicited a positive reaction. Smears failed to reveal the presence of Donovan bodies.

With fuadin therapy, the cutaneous lesions have almost completely healed and the swelling of the prepuce and penis has been considerably reduced.

DISCUSSION

DR. BORRIS A. KORNBLITH: Lymphedema in granuloma inguinale involves the question of lymphatic spread of this disease. The concept of the pseudobubo (Greenblatt, R. B.: Management of Chancroid, Granuloma Inguinale and Lymphogranuloma Venereum in General Practice, *Ven. Dis. Inform.* [supp. 19], 1943, pp. 1-43) and the occurrence of bubonuli (Sobel, N., and Pensky, N.: Bubonulus in Granuloma Inguinale, ARCH. DERMAT. & SYPH. **48**:494 [Nov.] 1943) and the presence of Donovan bodies in lymph nodes definitely point to a granuloma inguinale lymphangitis which induces edema both early and late in the disease when terminal scarring has taken place.

Inguinale lesions may often be looked on not as primary but as secondary to a small penile lesion, as Dr. Costello brought out.

Granuloma Inguinale, Involving the Anal Canal and Necessitating Colostomy. Presented by DR. HARRY C. SAUNDERS.

C. P., a Negro aged 29, was admitted to the dermatologic ward of Bellevue Hospital, complaining of ulceration in the anal region and the left groin of eight months' duration.

Examination reveals a large, linear, grayish red granulating ulcer extending from the left anterior superior spine of the ilium down the left inguinal region to the anus and involving the anal canal, with production of a large fistula and incontinence of feces. Numerous satellite fleshy granulating lesions are found on the scrotum.

Wassermann and Kahn reactions of the blood were negative. Hematologic examination showed a red blood cell count of less than 3,000,000 and a hemoglobin content of 50 per cent. Frei and Ducrey cutaneous tests elicited negative reactions. Stained smears from the lesion and histologic sections both showed the presence of many Donovan bodies.

The patient improved remarkably with fuadin treatment, but a colostomy was deemed necessary to insure complete healing of the anal and rectal tissues involved.

DISCUSSION

DR. DAVID BLOOM: This case is of interest, for involvement of the rectum is considered to occur only in lymphogranuloma venereum and not in granuloma inguinale.

Bullous Exfoliative Dermatitis Due to Arsenic. Presented by DR. LEO SPIEGEL.

P. B., a 61 year old Negro, was admitted to Bellevue Hospital because of a widespread bullous eruption of three weeks' duration. The patient stated that after a routine Wassermann test which elicited a positive reaction about a year and a half ago he began to receive weekly injections. He was given a total of twenty injections of a bismuth preparation and twenty of neoarsphenamine. After a six month rest period bismuth therapy was reinstituted, but after the fourth injection a pityriasis-rosea-like eruption developed. This was disregarded, and he was given another injection of the bismuth preparation. Soon after a severe bullous eruption developed. As no arsenicals had been administered for more than eight months and because of the nature of the eruption, the possibility of arsenic as the causative agent was not seriously entertained. A provisional diagnosis of pemphigus vulgaris was made, and the patient was referred to Bellevue Hospital for further investigation and treatment.

When admitted, the patient presented an extensive discrete and confluent bullous eruption covering the skin of the neck, trunk and upper and lower limbs but sparing the palms and soles. Two days later similar lesions appeared on the face and scalp and soon extended to involve the entire surface of the scalp. A clinical diagnosis of bullous arsenical dermatitis was made, and this was confirmed by the amount of arsenic present in the urine (0.25 mg. per thousand cubic centimeters of urine). Further studies are being made.

DISCUSSION

DR. CHARLES WOLF: This patient was in my service at the Morrisania Hospital prior to transfer. He showed large and small discrete bullae. The first impression was that one was dealing with pemphigus. Dr. Spiegel stressed the possibility of its being an arsenical allergic reaction. It has not been my experience that bullous lesions appear in crops as a result of arsenical dermatitis. Furthermore, this patient gives a history of having taken other drugs—e. g., laxatives. My impression is that this is an erythema multiforme bullosum of drug origin with a secondary dermatitis produced by arsenic.

DR. E. WILLIAM ABRAMOWITZ: This type of bullous dermatitis could be produced by arsenic even though no arsenical preparation had been used for months. The finding of arsenic in the urine is of little significance, even when it is measured in terms of a twenty-four hour specimen, unless the arsenic content in the diet and the use of local applications are known, among other things.

Dr. Spiegel's point is that the eruption is probably not due to bismuth but may be due to arsenic or may be a toxic eruption from some other source. I suggest symptomatic treatment. If the man got well and then were given another injection of an arsenical and the eruption recurred, it would be definite proof that ars was the cause, but one hesitates to do this.

DR. LEO SPIEGEL: I believe that this case sho have been presented for diagnosis with a question as whether it was bullous exfoliative dermatitis due arsenic pemphigus vulgaris. So far as I know, there no normal values for arsenic in the urine or blood. the two analyses of the urine of this patient, the val were well within supposed normal limits. The diagno in this case is not clear, and further observations m be made to arrive at a satisfactory diagnosis. D Cannon (Cannon, A. B.: Chronic Arsenical Poison *New York State J. Med.* **36**:219 [Feb. 15] 1936) stat that in a miscellaneous group comprising patients widely different ages, occupations and economic a social conditions arsenic was found in the blood a urine in amounts ranging from a trace up to 4.86 m per hundred grams of dried specimen. Sensitivity m play a role in producing this eruption, but I am mo inclined to believe that the patient has pemphig vulgaris.

Calcinosis Cutis with Telangiectasia. Presente by DR. MAURICE J. COSTELLO.

A. C., a 58 year old white woman, is presented fro the department of dermatology and syphilology, Bell vue Hospital. In 1931 she noted a painless swelling a the tip of the right thumb. About five years lat pain in the tips of the fingers was noticed, chiefly aft exposure to cold. This was relieved after immersi of the hands in cold water. The finger tips becom increasingly hard, and diminution of sensation gradual occurred.

Examination shows swelling and moderate distorti of the soft tissue at the distal end of the phalanx of th right third and fourth fingers and the left second an third fingers. The patient also shows rosacea.

Determinations of the blood chemistry showed a uri acid content of 3.6 mg. per hundred cubic centimeter a phosphate content of 3.8 mg., a phosphatase co tent of 4.1 mg. and a calcium content of 11 mg The basal metabolic rate was +7.2 per cent. Th blood count was within normal limits, and urinalysi showed no abnormalities. The Wassermann reaction of the blood was negative. Roentgen examination o the chest showed the heart to be enlarged in the trans verse diameter. The lungs showed interstitial change and fibrosis. Roentgen examination of the bones an joints revealed calcareous deposits in the bursas of bot shoulder girdles, in the radiohumeral bursas and in th peritrochanteric bursa of the left hip joint. No ab normality of the bones of the skull was noted. There were also evidences of hypertrophic changes in the cervicodorsal portion of the spine. The lumbar portion of the spine was normal. There was extensive calcifica tion of the descending aorta. Osteoarthritis of the metatarsophalangeal articulation of the right big toe was present. An analysis of material obtained by excision showed calcium phosphate, calcium carbonate and magnesium carbonate. The greatest portion of the deposit was composed of calcium phosphate.

DISCUSSION

DR. FRED WISE: Has treatment with parathyroid medication been of any value in cases of calcinosis cutis?

DR. MAX SCHEER: I should like to confirm what DR. COSTELLO said about the presence of rosacea-like

sions. About twenty years ago I had as a patient a woman with calcinosis cutis who also had a good deal of telangiectasia. This patient also showed some on the arms.

DR. OSCAR LEVIN: Besides the nodules, the skin showed purpuric and telangiectatic spots and areas of infiltration of the skin suggestive of scleroderma, especially striking on the upper extremities. I wish to call attention to the small petechiae and telangiectatic vessels in the palm and forearms, suggestive of damage to the small cutaneous vessels. The patient suggested that she was suffering from parathyroid disease, and she should have the phosphorus metabolism studied. I do not believe administration of parathyroid injection would be of value, and in fact it might prove dangerous and induce lithiasis. A diet low in phosphorus should be administered, with the elimination of eggs, milk and meat. Parathyroidectomy may affect the disorder favorably. The arthritis probably represents disturbances in the joints due to the general disease. Further studies should be made for the possible detection of endocrine and metabolic disturbances.

DR. MAURICE J. COSTELLO: This patient was thoroughly investigated. I should like to stress again the importance of the irregular rectangular areas of telangiectasia that occur on this patient's face, lips and extremities as part of the picture of cutaneous calcinosis, in addition to symptoms of Raynaud's phenomenon. I have read of cases in which the beneficial results of parathyroidectomy were spectacular. I should like to try the effect of dihydrotachysterol.

Calcinosis Cutis. Presented by DR. LOUIS TULIPAN.

J. T., a boy aged 15, noticed nodules on the left wrist about a year and a half ago, and similar lesions appeared on the left thumb and the back of the heels. Eight months ago he went to work as an iceman's helper. Similar hard lesions developed on the inner aspect of the right thumb and right middle finger. Occasionally one of these lesions would break down, become inflamed and discharge a chalky mixture. This would be associated with symptoms of fever. Five months ago some of these nodules were incised.

Recent examination reveals pea-sized to marble-sized calcified nodules, some covered by pinhead-sized keratotic plugs, on the inner side of the right thumb. There are about five such nodules in this group. Similar ones are present on the inner side of the right knee, above which is a thick, fibrous nodule with a central crater-like ulcer. On the ulnar side of the right middle finger is a hazelnut-sized thick fibrous nodule (pressure pad). On the backs of the heels are marble-sized, fibrous and calcified nodules. The skin in general is dry and scaly and in places shows keratotic plugs.

A general physical examination revealed normal conditions. The basal metabolic rate was —16 per cent.

Histologic examination showed the epidermis to be hyperplastic and undergoing pronounced cornification, with deposits of calcium among the cornified masses in a circumscribed area. The subcutaneous tissue did not contain any cutaneous appendages. Instead there were closely packed deposits of calcium within the connective tissue without any surrounding reaction.

DISCUSSION

DR. OSCAR LEVIN: The patient is suffering from localized areas of calcinosis, and trauma may aggravate the cutaneous lesions. In view of the fact that attention has been called to the possibility that this case is compensable, I may state that I believe a causal relationship may be established between the secondary lesions and the patient's occupation.

DR. LOUIS TULIPAN: There are supposed to be three types of calcinosis, localized, metabolic and metastatic. Two types have been presented tonight, my case, I believe, being of the localized type. The biopsy showed calcium in the connective tissue, and the basal metabolic rate was —16 per cent. The reason I say it is probably the localized type is that the patient has a xerodermatous skin and shows a pressure pad on the right middle finger. Another interesting fact is that calcium nodules and pressure pads developed after this boy began working on an ice truck.

Epidermolysis Bullosa. Presented by DR. TIMOTHY J. RIORDAN.

V. S., a white girl 3 months of age, was stated to have had "pimples" on the extremities at birth. These disappeared without treatment but reappeared on the eighth day as "blisters" on the feet and head. When first seen in the pediatric service of Bellevue Hospital, on the eleventh day after birth, the baby appeared acutely ill and presented numerous papules and pustules on the trunk and limbs as well as soft white patches in the mouth. She was given sulfadiazine internally for six days, sulfathiazole ointment locally to the pustular and infected lesions and paste of zinc oxide N. F. locally to the noninfected lesions. After the secondary infection had cleared, it was noted that there were two types of cutaneous lesions: The first was of a bullous nature and occurred on the back of the knees, toes and fingers. These lesions had two courses, the first productive of slow resolution terminating in atrophy and then hyperpigmentation. The second type of lesion also developed from bullae, but these later became verrucous, hypertrophic and crusted and were distributed on the fingers and toes, backs of the hands and feet, legs and forearms. The bullae did not usually appear in response to trauma, nor was exfoliation definitely observed.

Laboratory studies showed a hemoglobin content of 10.5 Gm., an erythrocyte count of 3,700,000 and a white blood cell count of 14,000, with 62 per cent polymorphonuclear leukocytes. The Wassermann reactions of the blood of parents and baby were negative. Roentgen examination of the long bones showed no abnormalities.

DISCUSSION

DR. E. WILLIAM ABRAMOWITZ: There is something unusual about this eruption, which does not quite fit in with epidermolysis bullosa. The lesions are definitely keratotic and give the impression not of ordinary bullae but of nevi of the angiokeratotic type.

DR. DAVID BLOOM: I have seen 2 such cases. In 1 the eruption occurred in several members of a family and was associated with dystrophy of the nails. Biopsy of apparently verrucous lesions showed the microscopic features of epidermolysis bullosa.

DR. TIMOTHY J. RIORDAN: When I first saw this child, on the eleventh day, the lesions looked more like linear nevus unilateralis; in the course of another ten days the eruption changed character and resembled a pyoderma. In the meantime the baby had received sulfonamide drugs and the lesions had become definitely bullous. The linear nevus configuration entirely dis-

appeared, leaving the crusted lesions seen tonight. A diagnosis of epidermolysis bullosa had been entertained at the beginning, although it was not the original working diagnosis; but the course of the disease suggested it more and more because bullae were actually seen. I have seen at least 2 such patients who had bullous impetigo which later became more typical of epidermolysis bullosa.

Keratosis Blennorrhagica. Presented by DR. FRANK C. COMBES.

J. H., a white man aged 44, is presented from Bellevue Hospital with a history of a purulent urethral discharge which occurred about three months prior to admission. This was followed two months later by a generalized cutaneous eruption and accompanied by malaise, loss of weight and polyarthritis.

Examination of the skin shows symmetric, discrete, round, raised, conical, reddish brown, dry keratotic lesions varying from 2 mm. to 1 cm. in diameter and located on the dorsal aspects of the wrists and hands, anterior aspects of the legs and both dorsal and plantar aspects of the feet. Similar but smaller and more confluent lesions are present on the lower half of the abdominal wall. Moist, oozing and erythematous lesions are found on the glans penis. The forehead is covered with psoriasiform lesions which extend to the anterior aspects of the scalp. Irregular erythematous lesions can be seen on the palate. These cutaneous lesions are associated with polyarthritis affecting chiefly the wrist and ankle joints. The patient complains of swelling, pain and limitation of movement of the ankle joints. There is no accompanying pyrexia.

The blood picture showed a moderate secondary anemia, with an erythrocyte count of 3,600,000 and a hemoglobin content of 64 per cent. The Wassermann and Kahn reactions of the blood were negative. Urinalysis showed many "threads." Culture of a smear from the urethra after prostatic massage showed the presence of gonococci. The complement fixation test for gonorrhea elicited a positive reaction. Smears from the lesions did not contain cocci. Histologic examination revealed changes similar to those seen in gonorrheal parakeratosis.

The patient has been treated by means of sulfathiazole, 1 Gm. daily for eight days, vitamin A (100,000 U. S. P. units) by mouth and physical therapy to the involved joints.

Perifolliculitis Abscedens et Suffodiens. Presented by DR. LOUIS TULIPAN.

R. W., a 26 year old Negress, was admitted to Bellevue Hospital with a history of a painful eruption on the scalp of two and a half years' duration. She stated that the eruption was getting worse in spite of the application of various salves.

Examination reveals numerous lesions involving nearly the entire surface of the scalp and consisting of boggy, fluctuant masses and many sinuses exuding a thick, yellowish pus, associated with alopecia and patchy scarrings. One boggy lesion extends down to involve the skin behind the right pinna. Similar lesions are found in both axillas and to a lesser extent on the hairy pubic region.

The blood and urine were essentially normal. Wassermann and Kahn reactions of the blood were negative. Smears and cultures from the lesions showed a predominance of staphylococci.

Great improvement followed oral administration of sulfathiazole for ten days (1 Gm. four times a day) plus more prolonged application of sulfathiazole ointment and powder locally.

DISCUSSION

DR. MAURICE J. COSTELLO: Several such cases have been observed, and it is my impression that patients with these deep-seated abscesses are improved by the oral administration of sulfathiazole, which is even more effective when combined with local application of 5 or 10 per cent sulfathiazole ointment. The drug should be administered over a long period if the patient is to be cured permanently.

DR. LOUIS TULIPAN: A 20 per cent solution in water was used, which was applied as wet compresses on gauze to the affected parts.

DR. E. WILLIAM ABRAMOWITZ: Sulfanilamide is not easily soluble in water (1 Gm. to 125 cc. of water). The material used must have been a suspension. The eruptions following use of sulfonamide compounds may be severe and unusually long in disappearing. The external use of the ointments for impetigo, furunculosis, etc., should be cautious. The department of health forbids the sale of any sulfonamide preparation for internal or external use without a physician's prescription.

DR. TIMOTHY J. RIORDAN: As Dr. Costello mentioned prolonged use of sulfonamide compounds, I thought of 1 case in which sulfathiazole was administered over a period of eight weeks and sulfathiazole powder, about 80 per cent, used locally; in this case we also used dressings wet with water containing zinc and copper sulfates (Alibour's water) and felt that the improvement was due chiefly to cleanliness and to the internal use of the sulfathiazole.

Dermatitis Medicamentosa (Phenolphthalein). Presented by DR. H. VICTOR MENDELSOHN.

J. S., a 29 year old Negro, was admitted to Bellevue Hospital on Nov. 30, 1943, complaining of a generalized cutaneous eruption of three days' duration. The patient stated that on the previous Saturday he had taken one Feen-a-mint pill and in about thirty minutes an itching eruption of the face developed. This soon spread to the rest of the body and was associated with chills, fever and malaise. He had had a similar but milder episode about one year ago following ingestion of some "vegetable compound."

Examination of the skin shows a discrete and confluent erythematous, urticarial and bullous eruption affecting the face, neck, trunk and limbs but sparing the palms and soles. The lesions are raised and erythematous at the periphery and hyperpigmented in the center, presenting a mottled appearance. There are no signs of sore throat or lesions on the mucous membranes or the genitals.

DISCUSSION

DR. ISADORE ROSEN: All of us agree that the eruption is due to the ingestion of phenolphthalein. When testing patients for a suspected drug eruption, one should use very small doses. I have seen serious complications follow the administration of large doses for this purpose.

DR. E. WILLIAM ABRAMOWITZ: The test dose of a drug to which the patient is sensitive should be small in order to avert severe reactions, as mentioned by Dr. Rosen. Mibelli years ago performed a biopsy of an area

viously the site of a fixed erythema from antipyrine was able to find pigment-bearing cells, although skin had assumed normal appearance. He attributed the tendency to react in situ to the presence these cells.

DR. H. VICTOR MENDELSOHN: Pigmentation is not prerequisite of a fixed drug eruption. The cutaneous ions of fixed drug eruptions appear as erythematous bullous), urticarial or eczematous plaques or patches may disappear without any pigmentation. I lieve that the clinical appearance of extensive pigentation three days after onset of the eruption is usual. This probably is due to the tendency of taneous lesions in Negroes to become hyperpigented. The numerous bullae and the presence of nstitutional symptoms are additional interesting atures of this case.

With regard to the development of cutaneous lesions e to drugs, other than those of the fixed variety, in person subject to a fixed eruption, I wish to call ention to my report of a case of fixed eruption in a ite woman who had previously had a scaly eruption e to neoarsphenamine (Mendelsohn, H. V.: Fixed ruption with an Extracutaneous Manifestation Due to ipharsen, ARCH. DERMAT. & SYPH. **41**:509 [March] 40). The fixed eruption was of the erythematous pe and left no pigmentation; the scaly eruption ermatitis?) did not recur in the same areas.

DR. E. WILLIAM ABRAMOWITZ: Pigmentation comonly observed in the erythematopigmentary type may t be present when the eruption is urticarial and lasts ly a few hours. Recurrent one-sided conjunctivitis and alized peripheral neuralgia, described by Jadassohn extracutaneous fixed effects, indicate that the term ixed" refers only to the tendency of a circumscribed ea or areas of tissue, at first apparently normal in ppearance and function, to react in situ on exposure the particular agent (allergen) to which it has come sensitized.

DR. H. VICTOR MENDELSOHN: I fully agree with Dr. Abramowitz' interpretation of the term "fixed" drug eruption.

DAVID BLOOM, M.D., *Chairman*

GEORGE M. LEWIS, M.D., *Secretary*

Jan. 4, 1944

Penicillin in the Treatment of Syphilis. Presented by JOHN F. MAHONEY, M.D., Senior Surgeon, United States Public Health Service; Director, Venereal Disease Research Laboratory, United States Marine Hospital, Staten Island, N. Y.

This report has been published elsewhere (Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis: A Preliminary Report, *Am. J. Pub. Health* **33**:1387 [Dec.] 1943; *Ven. Dis. Inform.* **24**:355 [Dec.] 1943).

DISCUSSION

DR. A. BENSON CANNON: I have listened with great interest to Dr. Mahoney's experiences in the treatment of early syphilis with penicillin. He deserves praise of high degree for the accurate and painstaking way in which he has conducted his experiments and congratulations for the results he has obtained. If I had any criticism to make, it would be that he has been too conservative in his claims for the drug. I do not know of any other remedy used in the treatment of early syphilis which has produced such results as he has presented tonight. I am further impressed with the fact that the drug is free from all injurious effects. It is most encouraging to learn that the action of penicillin on the early lesions of syphilis runs parallel with that of arsphenamine, so that after the first injection of the drug the chancre and all surface lesions are red and swollen, the lymph nodes swollen and tender, and the patient has a slight elevation in temperature, a headache, and is drowsy—reactions such as one expects on the first day of treatment with the arsenical preparations. Judging from Dr. Mahoney's observation in the few cases in which he has used penicillin, one is fairly safe in predicting that with this drug there is prospect of a real revolution in the practice of medicine. This section is indeed fortunate in having Dr. Mahoney tell us about his experiments with penicillin in the treatment of early syphilis, and I offer him our warm thanks.

DR. THEODORE ROSENTHAL: I think this section has heard tonight a pronouncement of historic importance. We should be grateful that Dr. Mahoney presented his paper here, for I believe this body is the first dermatosyphilologic society to hear it. From the history of the cases Dr. Mahoney has shown us tonight and from the records I saw recently when visiting his hospital, there is no question that this drug is remarkably effective. While traditionally all members of the medical profession should be conservative, nevertheless it does seem safe to say that with this new therapy one has a drug at one's disposal infinitely superior to those now possessed. We all hope that this type of treatment will become standardized and that additional supplies will soon be available for general use.

DR. E. WILLIAM ABRAMOWITZ: The action of this antibiotic is amazing, to say the least. There was a report about two weeks ago from the Mayo Clinic, where it was used in mice infected with the spirillum of relapsing fever, with equally startling results. I heard Dr. Mahoney about two weeks ago, and he neglected to include another interesting fact tonight. I believe that he said then that the penicillin had no action whatever on spirochetes suspended in penicillin, as viewed in the dark field, and yet in spite of that he went ahead and used it in syphilitic rabbits and the results were successful. That is the lesson all of us should learn—not to give up too soon. I want to congratulate Dr. Mahoney on his epoch-making discovery.

DR. DAVID BLOOM: I wish to thank Dr. Mahoney in the name of the Section of Dermatology and Syphilis of the New York Academy of Medicine for his presentation. I have been told by some of Dr. Mahoney's friends that he is as modest a scholar as one can be. This he has shown by the way he presented this important subject tonight.

Adenoma Sebaceum (Pringle); Lymphangioma Circumscriptum; Psoriasis. Presented by DR. FRANK VERO.

E. D., a white boy aged 16, is presented from Lincoln Hospital, with an eruption on the face, back, arms, legs and chest which has been present since birth. The patient was first seen in February 1941. There is no history of any similar cutaneous disease in the parents, four brothers and five sisters. There is no consanguinity. The patient's physical and mental development

have been normal, and he is now attending the third year of high school.

Examination shows a large number of discrete and closely grouped reddish and yellowish brown, pinhead-sized, firm, papular and small nodular lesions on the nose and alae. In the right sacral region is a palm-sized area of soft, easily compressible, small flesh-colored elevations.

Several lesions on the nose were treated by a private physician with the "electric needle," but these have since recurred. When seen again in October 1943, the patient showed a large number of small, papular, scaly lesions on the scalp, face, extremities and trunk.

Biopsy of the skin from the nose revealed a moderate atrophy of the epidermis in its middle portion and an irregular fibrosis of the dermis, the latter containing many hair follicles as well as many extremely large sebaceous glands closely clustered. This lesion was diagnosed as adenoma sebaceum (Pringle), and a lesion from the back as typical lymphangioma.

DISCUSSION

DR. MARTIN V. BOARDMAN (by invitation): The patient first came to Lincoln Hospital because of red "spots" on his nose. The eruption was similar to the one now present. The lesion on the sacrum was discovered accidentally. A biopsy made at Lincoln Hospital was reported as indicating "lymphangioma." Unfortunately, we have neither that report nor his old record and must resort to memory for the latter diagnosis.

The lesions on the nose were electrodesiccated by a dermatologist and faded for a while, only to recur.

DR. FRED WISE: I should have been unable to diagnose the lesion on the back as lymphangioma circumscriptum on clinical grounds, but I accept it on microscopic evidence. The coincidental existence of three different types of nevoid lesions is of interest.

DR. A. BENSON CANNON: It is interesting to have 2 cases of adenoma sebaceum presented before the section both of which are typical examples of the disease and yet strikingly different in their constitutional symptoms. One patient is bright and alert, while the other is decidedly backward mentally and epileptic. The latter patient has definite lesions in the brain, calcification of the inner table of the skull, changes in the optic chiasm and atrophy of one portion of the cerebrum. While one often speaks of patients with adenoma sebaceum who have mental symptoms, one is rarely able to present such a patient.

Milroy's Disease? Presented by DR. GEORGE M. LEWIS.

L. M., a white woman aged 22, appeared for the first time at the dermatologic clinic of the New York Hospital on Jan. 4, 1944, complaining of swelling of the left hand and both feet of fifteen years' duration. The swelling, which was first noted at the age of 7 years, subsided from time to time until five years ago, since when there have been no remissions. There is no associated pain. The family history is irrelevant.

On her admission to the New York Hospital one month previously there were revealed no pathologic alterations except a mild anemia. The urine was normal, and the serologic reactions of the blood were negative. The total serum protein was 6.7 Gm. per hundred cubic centimeters.

Physical examination shows a pitting edema of the left hand and both legs.

DISCUSSION

DR. DAVID BLOOM: I think the chronic lymphedema in this case fits in with that called Milroy-Nonne-Meige disease. Although involvement of the upper extremities is rare, cases with it have been described. If this disease was transmitted from one of the patient's parents it was not from the mother, for she remarried and the four children from this marriage are normal.

Fox-Fordyce Disease. Presented by DR. FRANK VERO.

G. W., a Negro aged 32, is presented from Vanderbilt Clinic, with an eruption affecting both axillas, the gluteal folds and the mons pubis, of eight months' duration. No medication has given relief. The patient gives a history of antisyphilitic treatments in the form of injections into the arms and hips.

The patient presents a large number of solitary and grouped firm papular lesions ranging in size from that of a pinhead to that of a millet seed, without any evidence of excoriations or scratch marks. There is some pigmentation in the affected areas. On the chest are multiple longitudinal keloidal scars.

The Wassermann reaction of the blood was negative.

Biopsy disclosed a specimen which had a large pilosebaceous organ into which a duct of an apocrine gland emptied. Hyperkeratosis, acanthosis and leukocytic infiltration of the epidermis were present. There were also edema and chronic inflammation of the cutis which was localized about the duct of the apocrine gland. The follicle was also involved. A parakeratotic plug with many polymorphonuclear leukocytes was seen. The lesion was one of an inflammatory nature without direct involvement of the acini.

The patient is presented for therapeutic suggestions. So far, all local medication and roentgen ray treatment have failed to give the patient relief.

DISCUSSION

DR. MAX SCHEER: This is an unusual disease in a male. I do not know the proportion of cases of Fox-Fordyce disease in Negroes and in white persons, but theoretically it should be greater in the former because of the large number and size of the apocrine glands in Negroes. I suggest the use of solid carbon dioxide.

DR. A. BENSON CANNON: I think this is a typical example of Fox-Fordyce disease, and I believe that it is rarely found in a full-blooded Negro. This is the first Negro I have seen with it although I have observed many persons of the white race with the disease. The only treatment I know of that has had any degree of success is the employment of destructive measures. Where practical, I advocate surgical excision of the affected parts in all cases that fail to respond to irradiation, desiccation or cauterization with acid. I have under treatment now a young woman with an extensive eruption of Fox-Fordyce disease who has had relief from filtered doses of radiation. Although she has been free from discomfort for almost a year, I am not sure that she will not have a recurrence of the itching. In addition to the radiation, I have painted the affected parts with 50 per cent phenol and neutralized it with alcohol.

DR. LEWIS B. ROBINSON: We had a Negress with Fox-Fordyce disease at Vanderbilt Clinic, and we decided to try progynon B. The effect was to make her much worse.

DR. SAMUEL M. KAUFMAN: I presented a case of Fox-Fordyce disease in a Jewish man aged 21, which

was published in the *New York State Journal of Medicine*. I looked up the literature at that time and found 3 cases on record—1 of Goodman, 1 of Fordyce and 1 in the European literature. My patient responded to roentgen irradiation and local application of antipruritic lotion.

Lupus Erythematosus of the Face Associated with Psoriasis of the Body. Presented by DR. E. W. ABRAMOWITZ.

C. S., a woman aged 62, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Sept. 8, 1943, with an eruption of the face of four years' duration and lesions of the body of five months' duration.

The eruption on the face involves the eyelids and the skin below the eyes and the nose, lips and sides of the chin. It consists of erythema and tiny scaly papules. The conjunctivas and eyelids are injected.

Below the left elbow and on the left buttock there is a nickel-sized scaly slightly raised erythematous plaque. The finger nails show slight pitting and longitudinal ridging.

Laboratory examinations, including those of urine, blood and cell count, gave normal results.

Biopsy on two occasions of the eruption on the face was reported as lupus erythematosus.

Treatment has consisted of liver extract and injections of a bismuth preparation.

DISCUSSION

DR. E. WILLIAM ABRAMOWITZ: With such a profuse eruption on the face, one would expect the bridge of the nose to be involved. There is no clinical appearance of atrophy. Although there are much redness and scaling, there is hardly any follicular gaping. Accompanying this, there is a recurring conjunctivitis, the nature of which I have not yet been able to determine. From the histologic standpoint, two biopsies of the lesions on the face have shown no picture of psoriasis but a fairly classic picture of lupus erythematosus. One thing that might be of help is that the patient stated the eruption occurred once before, about two years ago, when it appeared on the left side of the face only and disappeared after several injections of a bismuth preparation. The lesion on the face is most likely lupus erythematosus. It is possible that she has psoriasis of the body.

DR. PAUL GROSS: I think we cannot debate the diagnosis of the eruption of the face in view of the two biopsies giving the findings of lupus erythematosus. I am wondering, though, whether a section of a lesion on the body would prove the diagnosis of psoriasis. I presented a patient a few years ago who had extensive lupus erythematosus on the face and typical psoriasis on the legs and on the scalp. Both diagnoses were proved by biopsy. The interesting feature was that the patient had hepatic damage due to chronic alcoholism. Under treatment with liver injections, yeast, thiamine and pyroxidine, both eruptions cleared, a high serum cholesterol content returned to normal values and a positive cephalin flocculation reaction became negative.

DR. LOUIS TULIPAN: Although psoriasis is rather uncommon on the face, when it does occur there has frequently been a question between that diagnosis and lupus erythematosus. I think the two diseases resemble each other so much that it is difficult at times to make a differential diagnosis unless proved by biopsy. I agree with Dr. Gross that biopsy should be performed on other lesions on the rest of the body to determine whether or not they all represent the same process.

DR. E. WILLIAM ABRAMOWITZ: In addition, the patient also has an epithelioma on the right temple.

NEW YORK DERMATOLOGICAL SOCIETY

A. BENSON CANNON, M.D., *President*

GEORGE C. ANDREWS, M.D., *Secretary*

Dec. 21, 1943

Lipodystrophy in a Nevus. Presented by DR. GEORGE C. ANDREWS.

S. S., a 20 month old Jewish boy, has had a "birthmark" on the right shoulder and chest since birth.

In the nevus the subcutaneous tissue seems entirely absent. Through the thin atrophic skin over the nevus can be seen all the underlying blood vessels, giving the center of the lesion a bluish red hue. The child is slightly overweight but has the normal distribution of fat, except in the areas of the nevus.

Lipodystrophy in a nevus.

Treatment has been conservative on account of the peculiar atrophic features of the nevus. In July 1943 two areas, one at the tip of the shoulder, the other on the upper medial part of the chest, were treated with a 75 mg. flat radium element applicator with a 2 mm. brass filter in contact with the skin for three and one-half hours. In October 1943 the entire portion of the lesion on the chest was given 500 r of roentgen rays filtered with 2 mm. of aluminum. Treatment has caused regression of the tumor masses but no change in the atrophic condition of the skin.

The child is presented because of the peculiar disappearance of subcutaneous fat and the cutaneous atrophy, both of which were present before the radiation treatment. The nevus is probably a mixed nevus, involving both fat and blood vessels.

DISCUSSION

DR. HOWARD FOX: This is a most unusual nevus, resembling the one recently presented by Dr. Traub. It is apparently vascular and associated with considerable atrophy of the subcutaneous tissue.

DR. EUGENE F. TRAUB: Dr. Fox has drawn the comparison between this case and the one so closely resembling it that I presented at the October meeting. Dr. Andrews' patient presents an apparently much greater fat necrosis and loss of elastic and subcutaneous

tissues than my patient did, but the lesion lacks the peculiar stippling or reticulated network of superficial atrophy present in my patient. There is little doubt but that each is an example either of a peculiar vascular nevus combined with some other type of nevus or of a vascular nevus associated with or causing loss of subcutaneous tissue.

DR. R. H. RULISON: This is an extraordinary and most interesting mixed nevus. I wonder whether there is atrophy here or whether because of the abnormal structure there is a congenital absence of the fat tissue. I am not at all sure the terms "necrosis" and "atrophy" should be applied in this case. I think one should prove that some fat tissue was present and was lost. Otherwise the term "fat necrosis" does not apply.

DR. FRED WISE: I had the same impression as Dr. Rulison, that this lesion is accompanied by an absence of rather than atrophy of subcutaneous tissue.

A Case for Diagnosis (Lymphogranuloma Venereum?). Presented by DR. EUGENE F. TRAUB.

M. P., a single man aged 23, born in Puerto Rico, was first seen at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Nov. 30, 1943, because of a large granulomatous mass on the right buttock involving the anal region. This had begun about two years previously. He had received some kind of injections, without benefit. He said that he had never had a venereal infection. As a child, at the age of 3 years, he had received a severe kick in the left groin by a mule. This resulted in suppuration of the lymph nodes of that side, necessitating an operation. Several large scars are now to be seen in the left inguinal area.

The granulomatous mass on the right buttock measures about 3 to 4 inches (7.5 to 10 cm.) in length, 1½ inches (3.8 cm.) in width and about ¾ inch (1.9 cm.) in height. There is a constant moist discharge from this area. Extending over the buttocks are several peculiar brownish streaks which apparently represent deep blood or lymph vessels.

A Frei test performed on the right arm gave a negative control and an erythema at the site of the test which measured about 3 to 5 mm. in diameter and was slightly elevated. This erythematous area persisted for about one week and was looked on as a doubtfully positive reaction. A biopsy was reported as indicating that the lesion was an infected granuloma showing no evidence of tuberculosis or syphilis.

The patient was given eight filtered roentgen ray treatments of a relatively small dosage, together with six injections of 5 cc. of 1 per cent solution of antimony and potassium tartrate, with much improvement.

DISCUSSION

DR. R. H. RULISON: The lesion has apparently improved under roentgen ray treatment, and lymphogranuloma does not respond well to roentgen rays. I should think of granuloma inguinale in this case.

DR. FRED WISE: I think that a variety of interpretations can be made in the diagnosis of the lesion. One has been suggested, namely, lymphogranuloma venereum. Other diagnoses demanding elimination are tuberculosis and blastomycosis, as well as a form of tropical ulcer.

DR. GEORGE M. LEWIS: The appearance of this lesion impressed me as tuberculosis of the skin, but I believe that other diseases, such as granuloma inguinale, must also be considered.

DR. HOWARD FOX: The most likely diagnosis, in my opinion, is granuloma inguinale. Laboratory examinations have excluded a number of diseases which are simulated by the lesion. It is true that no Donovan bodies were found, but this often happens in cases of undoubted granuloma inguinale. The improvement after roentgen ray treatment favors the diagnosis of this disease. This patient, from Puerto Rico, has kinky hair and apparently has some Negro blood. This is significant, as granuloma inguinale is rarely seen in the white race.

DR. FRANK C. COMBES: I did not see this patient, but there seems to be some question about the diagnosis. I suggest a trial of Kornblith's new intracutaneous test for granuloma inguinale. A rather crude extract is used, but his results have been 100 per cent correct in the 40 or 50 cases in which it has been thus far tested.

DR. A. BENSON CANNON: I agree with Dr. Fox that the most likely diagnosis is granuloma inguinale. While I think that blastomycosis should be considered, as Dr. Wise has indicated, the lesion does not impress me as being due to that disease, inasmuch as there is no sinus formation, no exudate and no verrucous appearance. I should not consider tuberculosis as a likely cause for the same reasons and for the additional reason that there is no ulceration. I should think that the lesion might be excised, and the removed tissue could then be examined for Donovan bodies and studied histologically.

DR. EUGENE F. TRAUB: Does any one think that amount of erythema remaining at the site of the Frei test significant?

DR. FRANK C. COMBES: If the nodule did not measure 7 mm., it was not a positive reaction.

DR. EUGENE F. TRAUB: I should like to add one thing: Extending across the buttock on the side of the lesion there are three or four peculiar brownish streaks, which apparently are deep-seated and engorged lymph or blood vessels, indicating a rather deep involvement beyond the mere granuloma of the surface.

Adenoma Sebaceum (Pringle Type); Tuberous Sclerosis with Epilepsy (Epiloia); Mental Retardation; Fundus Changes. Presented by DR. A. BENSON CANNON.

L. M., a white boy aged 6 years, is presented from Vanderbilt Clinic, to which he was admitted for examination because of irritability and mental retardation. Tuberous sclerosis was suspected.

The child weighed 8 pounds 8 ounces (3,856 Gm.) at birth, which was a normal spontaneous delivery without complications. There is a sister, aged 14 years, who is normal. At the age of 5 months the boy was irritable and his left eye twitched. He vomited and had convulsions four or five times daily. Encephalograms showed idiopathic pyknolepsy, hypoplasia of the left cerebral hemisphere and hydrocephalus. The right side of the cortex was also said to be atrophied.

The eruption is said to have been first observed on his face three years ago and to have undergone no remarkable change. It consists of many small red telangiectatic papules scattered over the cheeks, nose and chin.

Roentgen examination of the skull showed intracranial (cerebral) calcification. Electroencephalographic studies showed an abnormal record suggesting left-sided large focus with convulsive signs. The ophthalmologic report

ated that the left fundus showed a lesion indicative of herous sclerosis near the fundus. The heart and kidneys showed no abnormalities. The kidneys were visualized by cystoscopy and urethral catheterization. Pyelograms showed conditions within normal limits.

Histologic examination of the skin of the face disclosed focal hyperplasia of the sebaceous glands, telangiectasia and perivascular round cell infiltration. The biopsy report was as follows: Sections of skin removed from the face disclosed a slight edema of the epidermis. The superficial capillaries of the cutis disclosed dilatation. There also appeared to be some proliferation of individual vessels with normal thickening. Surrounding these were infiltrations of mononuclear cells. The hair follicles were small, but the sebaceous glands appeared to be hyperplastic, although not enormously enlarged.

DISCUSSION

The members were in unanimous agreement with the diagnosis as presented.

Cutis Elastica. Presented by DR. A. BENSON CANNON.

C. C., a girl aged 11, of Irish descent, is presented from the Vanderbilt Clinic. Since her birth the patient has had "rubbery skin," and all the joints, particularly those of the fingers and to a lesser degree of the toes, can be hyperextended and flexed without pain. Hematomas have formed after slight trauma, often requiring aspiration. Falls have frequently resulted in wounds resembling cuts which have healed slowly and left scars. Since the age of 6 years she has had discolored scars on the knees. She has fallen frequently owing to the laxity of the joints, but her mother has noted no evidence of muscular weakness. She has difficulty in holding a pencil in her hand for long periods in school.

The patient has two brothers, one 14 and the other 9 years of age, with no evidence of similar disability. The family history is noncontributory, except that her maternal grandfather was able to "bend his fingers back."

Examination shows a bright, quick, slightly undernourished girl. On each knee over the patellar area there is a purplish, thin parchment-paper-like scar of about 1½ inches (3.8 cm.) in diameter. The margins of these scars are somewhat irregular. A few nodules can be palpated within the scars, but the underlying tissues feel thin when pressed against the patella. On the left elbow there is a similar scar ½ inch (1 cm.) in diameter. On the forehead are several white linear scars. The skin over the knees and elbows can be grasped between the fingers and extended several inches without pain. It returns to its normal position when tension is released. All of the fingers can be hyperextended, both actively and passively, without pain. The same is true of the toes to a lesser degree. The knees and elbows can be hyperextended about 15 degrees beyond normal. There is no evidence of muscular weakness.

The blood count was normal, with a normal platelet count (190,000). The Wassermann reaction was negative. Roentgenograms of the joints showed them to be normal. The amounts of creatine and creatinine excreted were respectively 19 mg. (0.019 Gm.) and 557 mg. (0.56 Gm.) per twenty-four hours. The bleeding time was three minutes, the clotting time seven minutes and the prothrombin time twenty-five and seven-tenths seconds (normal being eighteen to twenty-four seconds).

DISCUSSION

The members were in unanimous agreement with the diagnosis as presented.

Generalized Progressive Scleroderma, Six Years After Sympathectomy. Presented by DR. GEORGE M. LEWIS.

L. F., a woman missionary aged 57, first noticed a change in her hands and feet shortly after the birth of her fifth child, fifteen years ago. At first there was excessive coldness, sufficient to be uncomfortable. After several years she noticed a change in the texture of her fingers and to a lesser degree of her toes. In 1937, on her return to the United States from Turkey, there was definite hardness of the skin, with resultant difficulty in picking up objects and in executing fine movements. She underwent four successive sympathectomies and also another operation (hysterectomy). After those operations she experienced considerable symptomatic relief, particularly from the intractable coldness of the skin. For the past few years the disease has been progressive. The face and anterior portion of the scalp have been affected, and there is some interference with the normal masticating movements. She is bothered with the pain and inconvenience of small ulcerated areas which frequently appear over the tips of the fingers.

The examination discloses typical areas of scleroderma involving the fingers, the face, the scalp and to a less degree the toes. There is no noticeable ischemia or congestion.

DISCUSSION

DR. HOWARD FOX: My views are pessimistic regarding the treatment of progressive scleroderma. A considerable number of such patients were treated at the Mayo Clinic by sympathectomy, but, as the results were poor, the method, I understand, has been abandoned.

DR. FRANK C. COMBES: I recently talked this question over with a neurosurgeon. He did not approve of sympathectomy, but he had blocked sympathetic nerves with alcohol and procaine hydrochloride. It is a less difficult procedure, and he believes that it gives better results.

DR. LAIRD S. VAN DYCK (by invitation): Neostigmine methylsulfate was recommended for this disease by Dr. O'Leary at a meeting of the American Academy of Dermatology a few years ago. It was to be given in a series of injections. Has any one had any success with this drug or with any other in treatment of scleroderma?

DR. A. BENSON CANNON: Dr. Vero, at the Vanderbilt Clinic, has been using neostigmine methylsulfate in the treatment of scleroderma, with gratifying results. He showed me several patients who had been under treatment with the drug, and in each instance there had been improvement in the scleroderma.

Generalized Idiopathic Atrophy. Presented by DR. JOHN C. GRAHAM.

B. S., a woman aged 49, was presented before the Manhattan Dermatologic Society on Jan. 14, 1941 (ARCH. DERMAT. & SYPH. **44**:288 [Aug.] 1941).

Since that presentation, the patient has changed little, except that about twelve months ago a deep ulcer, which went down to the fascia, developed on the calf of her left leg.

DISCUSSION

DR. HOWARD FOX: This is the first case I can recall of diffuse atrophy covering every inch of the cutaneous surface.

DR. FRANK C. COMBES: I have never seen a case like this before. I was interested in the arthropathy. A number of years ago Oppenheim wrote me about the possibility of a focus of infection which produces a toxin acting on the elastic tissue. I wonder if there is a focus of infection here causing the arthritis and the atrophy.

DR. GEORGE C. ANDREWS: I should like to know whether this condition of the joints occurs in other cases of widespread idiopathic atrophy or whether it is unique in this case. I have never seen anything just like it before.

DR. GEORGE M. LEWIS: I wonder whether the eruption on the scalp is seborrheic dermatitis, favus or something else.

DR. FRED WISE: In regard to Dr. Andrews' question: About fifteen years ago I read a great deal of literature on the subject of cutaneous idiopathic atrophy and found that in many instances there was also in these patients a peculiar deformity of the hand which caused the index, middle and ring fingers to be deviated toward the ulnar side of the hand. It was a deformity but not an arthritic process per se.

DR. A. BENSON CANNON: The only cases of universal atrophy that I have seen that resembled this case were those that I reported following arsenical dermatitis. In them there was not only the atrophy but the reticulated capillary network in the skin and a brownish, macular pigmentation with alopecia. I suggest that this patient have the blood, urine and skin examined for arsenic.

DR. EUGENE F. TRAUB: The crusting, covering what I believe was described as superficial ulcers or erosions, presented by this patient raises an interesting point. Is it possible that these lesions appeared first as blisters in a process somewhat similar to that occurring in epidermolysis bullosa, a disease in which a disturbance of elastic tissue is thought to play a role? Does Dr. Graham know just how these crust-covered lesions developed? The patient stated that the lesions had begun as hemorrhages, not as blisters.

DR. JOHN C. GRAHAM: All the lesions I have seen have developed on hemorrhages. She gets a bruise; a hemorrhage develops, and then the skin breaks down to form an ulcer. There is no bleb formation. It is apparently a rather deep process. It sometimes goes down to the fascia. Dr. Webb treated her last year for one of these ulcers which went down to the fascia of the calf of the leg.

Localized Scleroderma with Calcification. Presented by DR. EUGENE F. TRAUB.

K. W., a woman aged 32, from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, first noticed the present condition in 1931. She injured the leg, with trauma to the shin bone, in a swimming pool. The same area was pierced by a rusty nail. Ichthammol ointment was applied, and she was given iodine drops by mouth. Roentgen examination of the bone showed it to be unaffected. A year later she was kicked in the abdomen by a horse, with a resulting discoloration of the skin on the left side of the abdomen. During the following five years there was no noticeable change except on the leg, where the skin became tight and shiny. During this period she suffered a contusion of the arm and the skin became discolored. During her pregnancy in 1938 her feet were swollen and there was some spreading of the affected area on the leg. She delivered a premature infant, and during lactation first noticed a spot on her hand, while the area on the leg became somewhat larger. Menses were irregular thereafter. A diagnosis was made at that time of scleroderma. The basal metabolic rate was —10 per cent, and the dextrose level of the blood was normal. At that time she received injections of pituitary gland extract and took thyroid extract and vitamin B internally. From 1939 to 1942, there was a continuous hardening of the skin of the affected leg and healing following an injury was slow although apparently complete. In May 1942 there was another injury to the leg, on the upper part of the shin. The skin was broken, and there was a watery discharge. This lesion did not heal, and another lesion developed immediately below the first one. In October there was ulceration at the middle portion of the shin. In January 1943 another ulcer developed under the second one, making two groups of two ulcers each on this leg.

In February 1943 the diagnosis of scleroderma was made at Vanderbilt Clinic. Investigation showed no tuberculous or cancerous tissue in the ulcers. The basal metabolic rate was + 16 per cent. She received ultraviolet radiation and took pancreatic extract internally. Scarlet red was applied to the lesions. At the Mary Fletcher Hospital, in June 1943, an Unna boot was applied. The larger ulcers were freshened at their edges, and vitamin A and D salve was applied daily. Spicules of calcium were removed from the ulcers on the leg during July and August. From September to the present time, the Unna boot has been applied weekly and local applications have consisted of vitamin A and D ointment with sulfonamide drugs and solution of methylrosaniline (gentian violet). There has been no noticeable shrinking in size of the ulcers. They have continued to discharge, and there are reddening and blistering of the skin.

Roentgenograms in June and November 1943 showed extensive calcification in the subcutaneous tissues, with no appreciable changes in the second examination. No changes were noted within the bones themselves.

In my opinion there has been some progress locally, with less irritation and no stiffness of the skin as previously noticed. There has seemed to be some relation between the nervous system and the ulcerations, as ulceration occurs when nervous tension is greatest. Exercise improves the condition.

DISCUSSION

DR. FRANK C. COMBES: I agree with the diagnosis. Calcification or calcareous degeneration or replacement with calcium is not uncommon in this localized type of scleroderma. In the roentgenogram there was a suggestion in places, I thought, of periostitis. The patient has had so much injury that some periostitis, of course, should be expected, but there is no doubt that there is some deposit of calcium, too, in the soft tissues.

DR. LAIRD S. VAN DYCK (by invitation): The presence of these spicules of calcium in the soft tissue would indicate an increased parathyroid activity. I wonder whether calcium studies of the blood showed any increase.

DR. THOMAS N. GRAHAM (by invitation): I had occasion to study the literature on calcinosis several years ago in connection with a case reported from the Knickerbocker Hospital (Graham, T. N.: Metabolic Cutaneous Calcinosis: Report of a Case with Sclero-

erma, ARCH. DERMAT. & SYPH. **41**:864 [May] 1940). Dr. Traub's patient, I believe, has the metabolic type of calcinosis, in which the blood calcium value is normal. My patient had calcium deposits over many of the bones, as shown by roentgenograms of the entire skeletal structure. There was involvement of one leg almost identical with that in the patient seen today. Fragments of calcium were discharged from the ulcer, which would subsequently heal, only to recur with a further discharge of calcium particles. I believe, therefore, that surgical excision of the area would probably not effect a cure, as it is likely that new calcium deposits would produce a recurrence of the ulcer.

DR. G. F. MACHACEK (by invitation): It would be interesting to prove whether this is an ordinary calcinosis or an osteomatosis. In a recent case a disease which was diagnosed as a generalized calcinosis was found on study not to be that but to be a true osteomatosis. It looked much like the condition of this patient except that it was generalized. The deposits were true bone.

DR. J. LOWRY MILLER (by invitation): I agree with Dr. Graham. The blood calcium value in this case was normal. The process is probably a metabolic calcinosis.

DR. HOWARD FOX: The presence of bony deposits (osteomas) in the skin was mentioned by Dr. Machacek. True osseous formation has been observed in the skin, but only on extremely rare occasions, as opposed to deposits of calcium, which are not rare.

DR. EUGENE F. TRAUB: No recent hematologic studies have been made, but results of those reported from the Vanderbilt Clinic about a year ago are said to have been normal. One of the chief reasons for presentation was that the question of an operation and skin graft as a method of therapy had been brought up. I did not wish to advise or even approve an operation, for the reason stated by Dr. Graham. Even if a graft should take, which is open to some question, there is no assurance that the same process might not occur again, either at the same site or at the margin. It appears that the members are in agreement in advising against operative procedure. Another question is that of roentgen therapy. I have mentioned before that in cases of localized scleroderma small doses of roentgen rays have apparently proved beneficial. This has apparently been something of a surprise to some of the members who evidently are not familiar with the literature. A not infrequent method of treatment recommended in Europe has been application of a paste containing a thorium salt, and roentgen rays and radium have also been employed. The radioactive pastes have apparently been of considerable benefit, and in cases in which the lesions have been comparatively small I have seen them disappear after relatively small doses of radiation. Therefore, I wonder if any one can think of any contraindication to giving such therapy a trial in this case. I realize that because of the calcified spicules that are continually being extruded from the ulcers healing by any method may be doubtful until such time as these foreign body particles are eliminated.

Multiple Steatomas (Steatocystoma Multiplex). Presented by DR. GEORGE M. LEWIS and DR. HANS J. SCHWARTZ.

E. W., a widow aged 31, is presented from the New York Hospital. She has had acne vulgaris for many years. About eight or nine years ago small skin-colored lesions appeared on the front of her neck and later on the chest and back. Some of the lesions have increased in size. Other lesions have become purulent and after drainage have disappeared, leaving scars. The lesions are of various sizes, cystic and subcutaneous, not involving the skin, which appears normal. There are many scars of healed lesions and some scars where lesions have been incised. Some bluish tones are seen in some lesions, and a yellowish color is observed in others. The patient has arrested pulmonary tuberculosis. The Wassermann reaction was negative. A biopsy showed a dilated acinus, which appeared to be a dilated sweat gland.

DISCUSSION

DR. G. F. MACHACEK (by invitation): This is a small cyst with a thin epithelial lining, one cell thick as far as one can tell. This is not unusual in cases of steatocystoma. It differentiates it from the ordinary sebaceous cyst, which is thicker walled, with a piled-up stratified squamous epithelial lining.

DR. HANS J. SCHWARTZ: I saw this woman a few weeks ago in the wards of New York Hospital and made a clinical diagnosis at that time of steatocystoma multiplex, and I still adhere to that diagnosis in spite of a histologic report of syringocystoma.

DR. FRED WISE: I agree with the diagnosis of steatocystoma.

DR. JOHN C. GRAHAM: I agree with the diagnosis of steatocystoma.

DR. FRANK C. COMBES: Is there not some difference between sebaceous cyst and steatocystoma genetically? Is steatocystoma of nevoid origin?

DR. G. F. MACHACEK (by invitation): One cannot tell clinically if the difference is genetic or if the steatocystoma is nevoid in origin.

DR. LAIRD S. VAN DYCK (by invitation): I thought I saw on this patient's chest a few pinhead-sized nodules which could possibly be syringocystoma, but the larger nodules I think are undoubtedly steatocystomas.

Subacute Disseminated Lupus Erythematosus (Subsequent Report). Presented by DR. HOWARD FOX.

Miss M. A. Y., presented on Nov. 23, 1943 as having subacute lupus erythematosus disseminatus, was hospitalized for three weeks and given a course of sulfanilamide for one week. Neither this treatment nor a transfusion of 500 cc. of blood caused any benefit. A roentgenogram showed chronic sinusitis. The maxillary sinuses were irrigated on three occasions, and slight improvement in her general condition followed.

Book Reviews

Allergy. By Erich Urbach, M.D., with the collaboration of Philip M. Gottlieb, M.D. Cloth. Price, $12. Pp. 1,073, with 396 plates. New York: Grune & Stratton, 1943.

Many texts and monographs have been written on allergy. Most of these have devoted particular attention to this phenomenon as it applies to the various so-called allergic shock organs and to allergy as a specific etiologic concept. In this book, which is the most extensive and comprehensive presentation of this subject published in the English language, the immunologist, pathologist, internist, pediatrist, dermatologist, rhinologist, ophthalmologist and others will find allergy and atopy as it applies to his particular specialty adequately considered from an etiologic, pathologic, therapeutic and prophylactic viewpoint.

The Continental training of the author is evident throughout the entire text in his handling of detail and his practical application of the problem of sensitivity to the individual patient. He has attempted to present an impartial interpretation of the conflicting views on the various controversial questions but has not neglected to express his own personal opinions and critical comments whenever necessary. These opinions are based on twenty-five years of intensive experimental and clinical experience with large and varied material in the field of allergy.

His conception of the subject is somewhat broader than that of many immunologists in that he attempts in all instances of sensitivity, in addition to eliminating the allergen, to determine the general influences responsible for the production and maintenance of the disease. In other words, he recognizes that hyposensitization in treatment without elimination of the factors predisposing to allergy is in many instances only of temporary value.

The substance of the text is grouped in thirty chapters, which are divided into three parts and an appendix. The first part is devoted to a consideration of the fundamentals of allergy, its general diagnosis and methods of treatment. This section is opened by a historic survey, followed by a complete and comprehensive consideration of the basic principles of allergy, so arranged and paragraphed as to appeal to the most critical reader. Part II is devoted to consideration of the more common etiologic agents, while Part III comprises a discussion of the various diseases from the clinical and therapeutic viewpoints. The latter section is divided into several chapters, each devoted to a specific allergic shock organ; namely, the upper respiratory tract, the lower respiratory tract and the gastrointestinal tract, the gallbladder, skin, nervous system, eye, cardiovascular system, joints, urinary tract and genital organs and allergic diseases of newborn infants, children and the aged. The appendix includes a series of detailed clinical record forms for the allergic patient as well as tables of concentration for the substances used in patch tests.

The dermatologist will find much valuable information and useful knowledge in the section devoted to allergic diseases of the skin. In conformity with the importance of the skin as an allergic shock organ, over one hundred pages are allotted to a consideration of this subject. Since the author's primary interest is in cutaneous disease, it is natural that his handling of allergy as it relates to various dermatoses should be presented in such fashion as to be of interest and practical value to physicians whose particular interest lies in this specialty.

As the treatise is the most complete work published on allergy in the last decade, the reader should naturally be interested in the index and bibliography. The former is complete and includes not only a compilation of subject matter but a list of author references.

Numerous illustrations embellish the text. In addition, over 2,300 references from the literature are presented in the form of footnotes, which are appropriately cross referenced so as to avoid duplication and repetition in the text.

A Hundred Years of Medicine. By C. D. Haagensen and Wyndham E. B. Lloyd. Price $3.75. Pp. xii plus 444, with illustrations. New York: Sheridan House, 1943.

This book was originally published in London in 1936 as part of Duckworth's "one hundred years" series, and at that time it was written by W. E. B. Lloyd. The present volume has been changed in both context and scope. It has been greatly enlarged and the greater part of it rewritten, with emphasis on the American scene. An attempt to cover with a broad brush the medical history of the past one hundred years, to limit it to four hundred and forty-four pages and at the same time to avoid omission of important subjects is a difficult, if not impossible, task.

In the chapter on diseases of the heart (page 192, eleventh line from the bottom) Jean-Nicholas Corvisart is described as a distinguished pathologist, but no mention is made of the immense amount of clinical work done by him in cardiac diseases and physical diagnosis. Medical historians have rightly described Corvisart as the father of modern cardiology. Much of the later work done by his pupil Bouillaud in endocarditis is founded on similar work done by Corvisart. On the same page Bouillaud is repeatedly called Bouillard, which is erroneous.

The specialty of dermatology made all of its progress in the past one hundred years, yet it is not mentioned in the book; the same is true of psychiatry, which is also ignored. Ophthalmology is given slightly over two pages, while otorhinolaryngology commands eleven. The illustrations are excellently reproduced, but, unfortunately, the majority of them are misplaced. The portrait of Ehrlich is found in the chapter on vitamins, forty-two pages away from the description of his vital discovery in chemotherapy. Laennec's portrait is placed in the chapter relating to diabetes, while Banting's is in the chapter on anesthesia; Semmelweis' is in the chapter on otology. Pierre and Marie Curie are placed thirty-two pages away from the account of their discovery of the element in the development of which they labored a life time. Harvey Cushing serves as a frontispiece for the chapter on trained nurses.

There are a number of typographic errors. In the paragraph on the "massive dose" method of treating syphilis Louis Chargin's name is mispelled "Chagrin" —an important lapse when it comes to proper names.

In spite of his criticism, this reviewer is of the opinion that the book is well worth reading and contains interesting and important facts which should stimulate interest in medical history, not only in the medical student but in the medical man as well.

the local problem in ACNE VULGARIS

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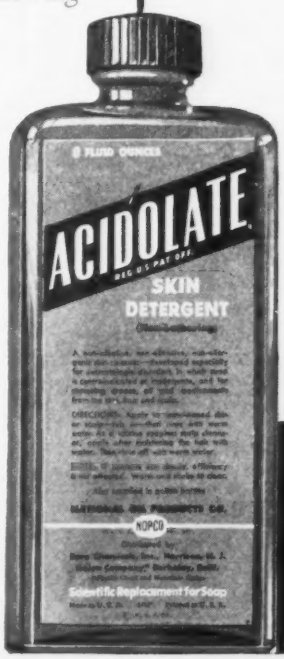

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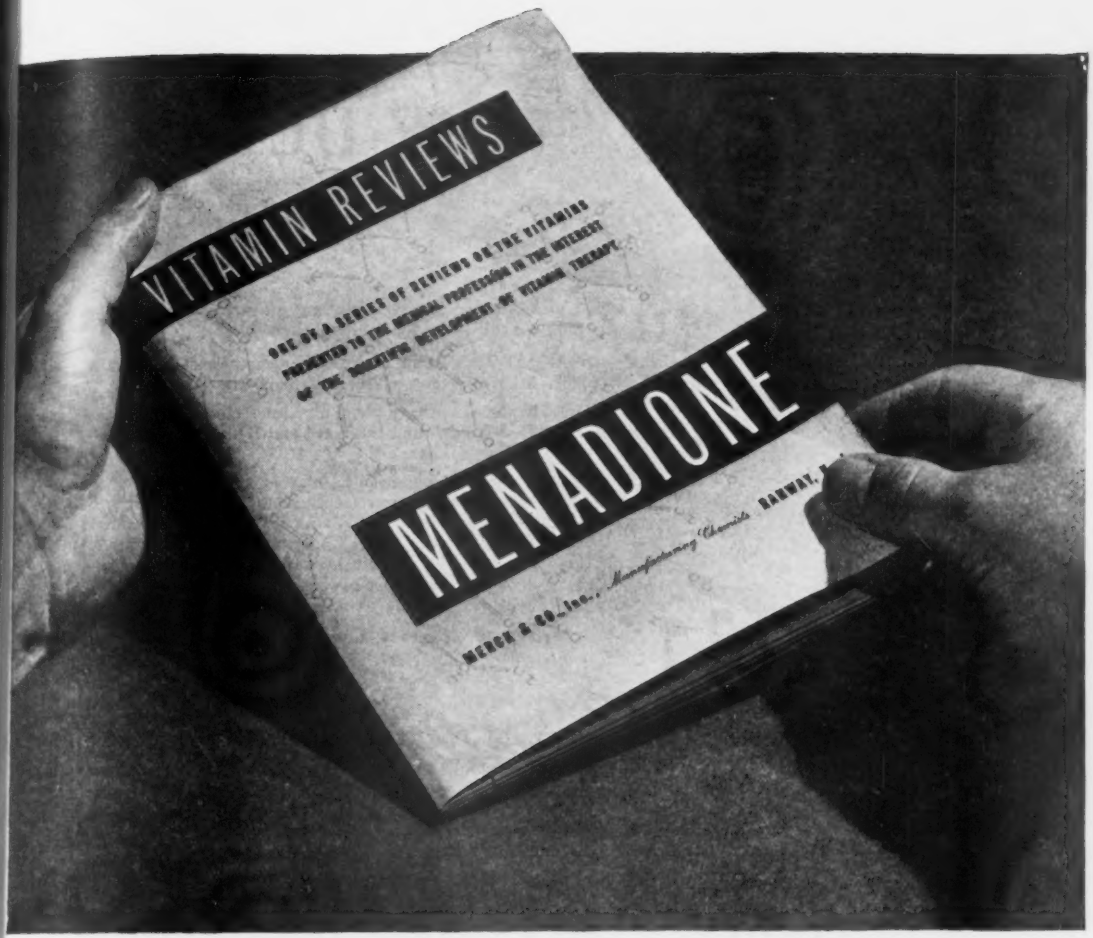
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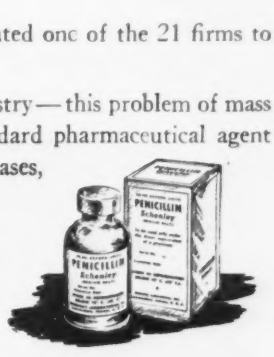

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